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ARCHIVES OF PATHOLOGY

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EXPERIMENTAL RHEUMATIC ARTERITIS *

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In rheumatism, the large and the small arteries, as well as the joints and the heart, are sites of acute inflammation. Certain portions of the arterial system, according to Klotz,[1] are attacked in this disease as frequently as is the musculature of the heart. This type of arteritis is considered by some observers to be specific for arteries infected with rheumatic virus.

In fifteen cases of rheumatism coming to Klotz [1] for necropsy, he found that the arterial injury was confined primarily to the regions of the vaso vasorum. In these regions, there was a loss of muscle and of elastic connective tissue. In a further study in another series of cases, he found the inflammatory lesion limited to the adventitia and media. The intima did not show involvement except as a later secondary injury over the inflamed media. The lesion in the adventitia and media consisted of an exudate along the small nutrient vessels. This exudate was composed chiefly of lymphocytes and plasma cells, but polymorphonuclear leukocytes sometimes were present in large numbers. The exudative reaction was accompanied by a destruction of muscle and elastic connective tissue.

In seventy-six cases of acute rheumatic fever, Pappenheimer and von Glahn [2] found the distinctive lesion of the aorta to be a scar, often acellular, in the region of the nutrient vessels in the media. Large mononuclear and multinucleated cells were arranged irregularly or in nodules in the adventitia. This type of arterial lesion was not found in a comparative study of seventy-seven nonrheumatic cases, with the exception of one, in which death resulted from pneumococcic meningitis. In this case, Aschoff bodies were present in the heart. These observers considered the cellular reaction to be a result of lysis of the collagenic fibers. In a later study of the aorta in a case of acute rheumatic fever,

* From the Department of Pathology, University of Minnesota.

1. Klotz, O.: Rheumatic Fever and the Arteries, Tr. Am. Phys. **27**:181, 1912; Arterial Lesions Associated with Rheumatic Fever, J. Path. & Bact. **18**:259, 1913.

2. Pappenheimer, A. M., and von Glahn, W. C.: Lesions of the Aorta Associated with Acute Rheumatic Fever, and with Chronic Cardiac Disease of Rheumatic Origin, J. Med. Research **44**:489, 1924; A Case of Rheumatic Aortitis with Early Lesions in the Media, Am. J. Path. **2**:15, 1926; Specific Lesions of the Peripheral Blood Vessels in Rheumatism, ibid., p. 235.

they found a reaction in the arteries similar to that reported in their first cases but marked, in addition, by the presence of large multinucleated cells in the media, as well as in the adventitia.

In a study of the effect of rheumatic infection on the smaller vessels in various parts of the body, von Glahn and Pappenheimer found what they described as specific lesions in the smaller arteries in ten of forty-seven cases examined. In this specific arteritis, the endothelium became swollen and basophilic. Sometimes it was raised from its basement membrane by a coagulated exudate. The vessel wall became thickened by the infiltration of fibrin. Evidence of cellular necrosis was present in all parts of the vessel wall. Extravasated red blood cells could be seen either immediately beneath the endothelium or in the meshes of the fibrin. Exterior to the necrotic wall, there was a cellular exudate, many cells of which were polymorphonuclear leukocytes showing various stages of necrosis. In this cellular zone, there were also cells with large vesicular nuclei, plasma cells, eosinophils and the cells of young connective tissue. Among the threads of fibrin were seen branching or polygonal mononuclear or multinucleated cells with deeply staining nuclei.

The arterial injury described by Klotz and by Pappenheimer and von Glahn consisted of an exudative and proliferative change and a scar, which probably followed the cellular injury. The cellular reaction corresponded to that found in rheumatic inflammation in the Aschoff bodies and to the inflammation found in other parts of the body in cases of acute rheumatic fever. The cellular exudate consisted of plasma cells, lymphocytes, eosinophils and polymorphonuclear leukocytes. There was also the fibrinous exudate which was observed by Frank [3] and Swift [4] in the subcutaneous rheumatic nodules. The proliferative reaction was made up of large and irregular mononuclear or multinucleated cells, apparently similar to the large cells in the Aschoff bodies. A retrogressive change or necrosis was also noted. This necrotic condition was emphasized by Fraenkel [5] in the Aschoff bodies and by Frank in the subcutaneous rheumatic nodule. The reaction appeared in all respects similar to that found in rheumatic infection in other parts of the body.

In this paper, a description is given of certain arterial lesions that were produced experimentally. Streptococci had been repeatedly injected into monkeys in an effort to produce glomerulonephritis. Microscopic examination showed in the kidneys of two of the monkeys vascular changes which bore a resemblance to the lesions described by

3. Frank, P.: Ueber den Rheumatismus nodosus mit besonderer Berücksichtigung des pathologischanatomischen Befundes, Berl. klin. Wchnschr. **49**: 1358, 1912.

4. Swift, H. F.: Pathogenesis of Rheumatism, J. Exper. Med. **39**:497, 1924.

5. Fraenkel, E.: Ueber Myocarditis rheumatica, Beitr. z. path. Anat. u. allg. Pathol. **52**:597, 1912.

Klotz and by Pappenheimer and von Glahn. One of the two monkeys had received an intravenous injection of a strain of *Streptococcus viridans,* isolated from the blood of a patient having acute rheumatic fever. The monkey had received 33 large injections over a period of 108 days. Death had resulted, apparently, from chronic glomerulonephritis.[6] The second monkey had also had repeated injections of another strain of *Streptococcus viridans.* This streptococcus had been isolated at necropsy from the blood of a patient dying with acute rheumatic endocarditis. The monkey had received large doses in thirty-nine different injections. Of the injections, thirty-two were intravenous and seven were made

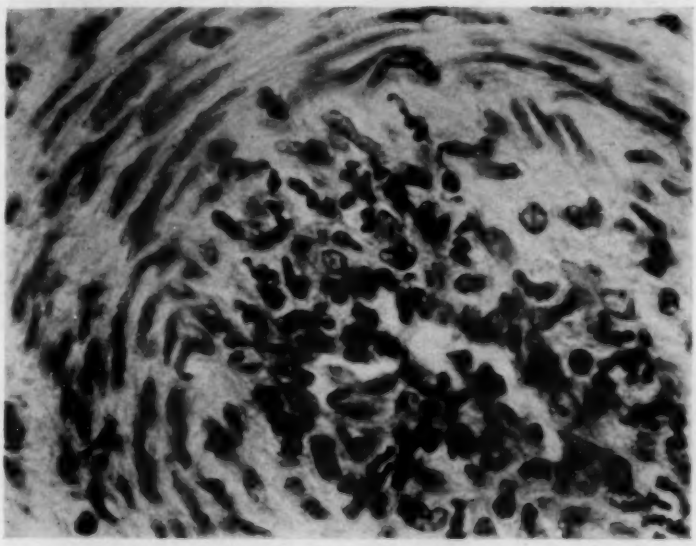

Fig. 1.—Arteritis (rabbit) chiefly in the intima.

through the left ventricle into the left ventricular cavity. The animal lived, from the time of the first injection to the time of death, a little over twenty-three months.

In another series of experiments in which many rabbits had had streptococci injected intravenously or subcutaneously in the effort to produce, experimentally, Aschoff bodies and subcutaneous rheumatic nodules, similar examples of arteritis were noted. This arteritis was commonly found in the hearts of rabbits into which streptococci had been injected intravenously, and practically always in the subcutaneous tissues of rabbits into which the streptococci had been injected subcutaneously. The organisms used were strains of *Streptococcus viridans* iso-

6. Bell, E. T.; Clawson, B. J., and Hartzell, T. B.: Experimental Glomerulonephritis, Am. J. Path. **1**:247, 1925.

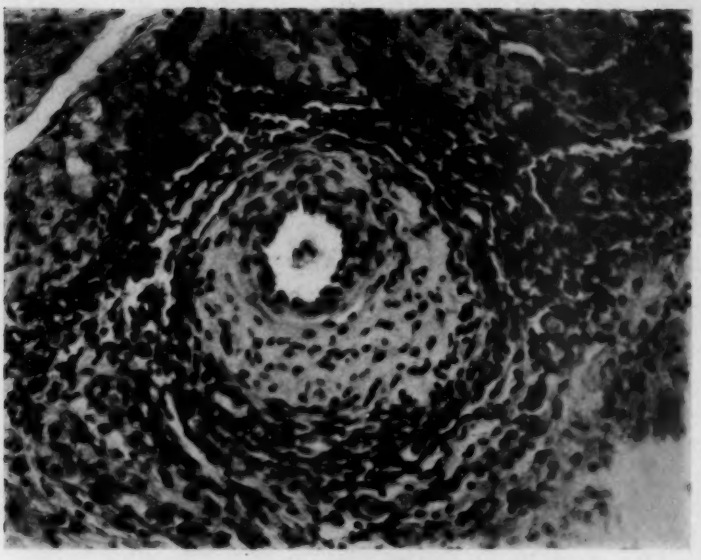

Fig. 2.—Arteritis (rabbit) chiefly in the adventitia.

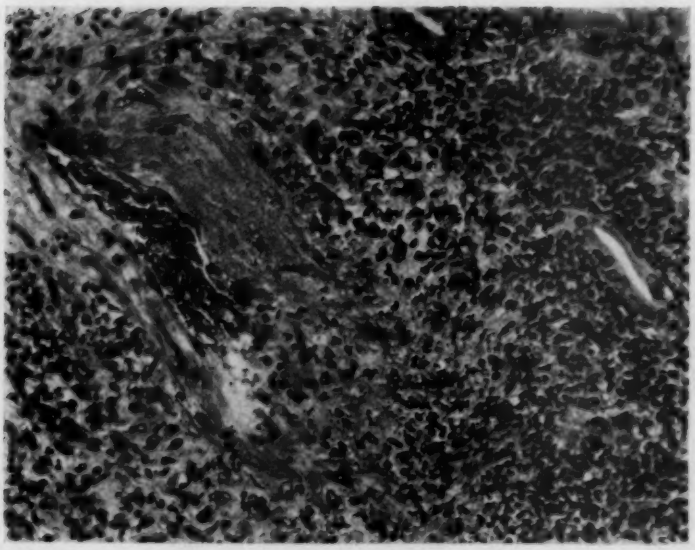

Fig. 3.—Arteritis (monkey) involving all layers of the arterial wall.

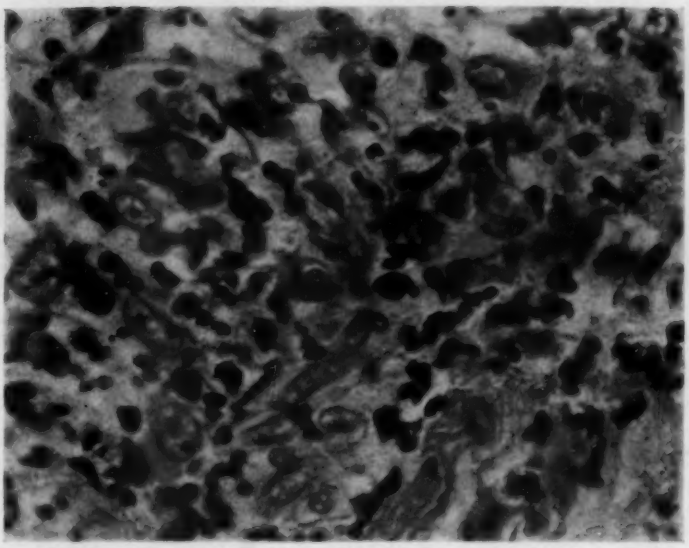

Fig. 4.—High magnification of the arteritis of the arterial wall shown in figure 3, showing the cellular reaction.

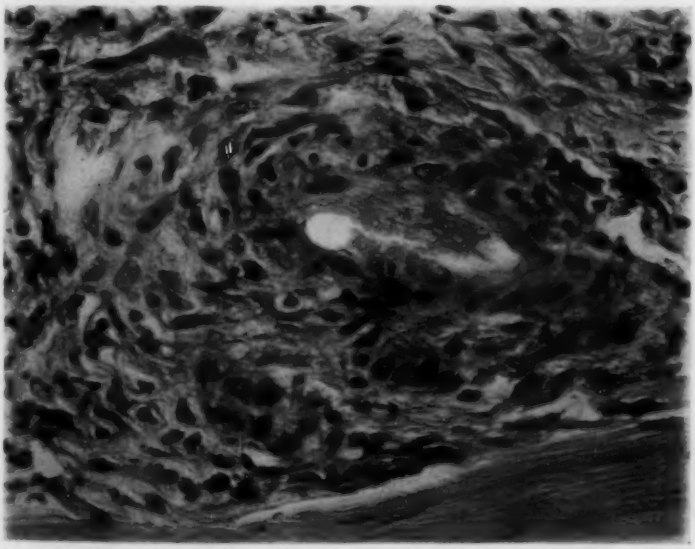

Fig. 5.—Proliferative arteritis of the subcutaneous tissue of a rabbit.

lated from the blood of patients with acute rheumatic or subacute bacterial endocarditis, except two, which were isolated from the pus of infected sinuses.

The degree of arteritis noted, varied. In many arteries, the reaction was confined chiefly to the intima (fig. 1), while in others it was primarily in the adventitia (fig. 2). In some, all parts of the vessel wall were involved (fig. 3).

As in the arteries studied by Klotz, and by Pappenheimer and von Glahn, exudative, proliferative and retrogressive changes were noted. Polymorphonuclear leukocytes in various stages of necrosis were present. Lymphocytes were to be observed especially in the adventitia of small vessels in the subcutaneous tissues. A hyalinized substance, apparently consisting of necrotic vessel wall and fibrin, was seen in some of the vessels (fig. 3). The elastic tissue had become broken up into segments. Scattered throughout the vessel wall were red blood cells. The chief reaction was the proliferation of cells. Large and irregular proliferating cells were to be found in all layers of the vessel, but they were especially conspicuous in the media and the adventitia (figs. 4 and 5). Some of these cells were multinucleated. Some nuclei were vesicular and others, hyperchromatic. The nuclei in many cells were curled and twisted and resembled the epithelioid cells in the tubercle. The perivascular infiltration of round cells in the subcutaneous tissues had a marked resemblance to the perivascular infiltration in syphilitic lesions.

The result of these experiments showed that by injecting streptococci into rabbits and monkeys lesions could commonly be produced which morphologically appeared similar to the rheumatic lesions in man described by Klotz, and by Pappenheimer and von Glahn, as specific for an infection with rheumatic virus. The morphology of the cellular reaction in this experimental arteritis was also similar to that found in the Aschoff nodule and in rheumatic inflammation in other parts of the body.

This similarity in inflammatory reaction between the arteritis commonly found in cases of acute rheumatic fever and the arteritis produced in animals by the injection of streptococci further suggests a causal relation between the streptococci and the rheumatic infection.

ANGIOBLASTIC MENINGIOMAS*

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INTRODUCTION

In a recent monograph [4] on the subject of the blood-vessel tumors of the brain, these lesions were subdivided into the *angiomatous malformations* and the *angioblastomas,* the latter being true neoplasms composed of the blood-vessel-forming elements.

Whereas the angiomatous malformations were found to be far more common in the cerebral hemispheres, the angioblastomas, on the other hand, were practically confined to the cerebellum; and though the literature contains reports of a few cerebral cases that seem indubitable, they are so rare that they merely serve to emphasize the preponderance of the angioblastic tumors in the hindbrain.

These cerebellar angioblastomas may be of several sorts. In gross they are either predominantly solid lesions or predominantly cystic, a small, sometimes minute, mural nodule serving to betray their nature, the tumors of the latter sort often being mesially placed lesions which apparently arise from a vascular anlage adjacent to the posterior portion of the fourth ventricle. Histologically, they are divisible into three main groups: those essentially capillary, those essentially cellular, and those essentially cavernous. Though most of the tumors contain areas representative of all of these three types, one peculiarity, however, is characteristic of them all, namely, *an intercellular network of reticulin that permeates the lesions and is best shown when the sections are stained by Perdrau's method.* This characteristic, in addition to their general microscopic structure, serves readily to differentiate the hemangioblastomas from highly vascular gliomas or meningiomas with which they may easily be confused.

Some authors, notably Lindau [7] who has contributed much to our knowledge of the hemangioblastomas, go so far as to state that they never occur in the cerebrum. With this view, our experience is largely in accord, and though the literature contains descriptions of a few so-called blood-vessel tumors that have been found in the cerebrum, we are inclined to regard these, with one or two possible exceptions, as hemangiomatous malformations rather than tumors.

We nevertheless confess to have been greatly puzzled as to the proper classification of a particular tumor (case 3) that had first been

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disclosed in the course of a cerebellar operation and been regarded as a probable meningioma. The tumor subsequently became aneurysmal in character, acquired sarcomatous tendencies, spread into the occipital lobe, and when tissue was finally secured for study, it was found to resemble a hemangioma rather than the usual meningeal tumor.

Aroused by this observation, a histologic re-examination of our series of meningiomas has been made by one of us (Eisenhardt), new sections of all these tumors having for the first time been stained, according to routine, by Perdrau's method. This re-examination, to our great interest, led to the disclosure that two other of the supposedly vascular meningiomas in our collection had a practically identical microscopic structure with the same reticular network that had characterized the cerebellar hemangioblastomas; and in a fourth case, there appeared to be transitional evidences in this same direction.

This discovery has caused us trouble, for we did not know whether to lengthen our treatise on the blood-vessel tumors by the inclusion of these cases as a type of undescribed cerebral angioblastoma or to report them, as we have finally decided to do, separately. We have been led to this decision because of our feeling that these tumors were after all not primarily pure angioblastomas, as were those in the intracerebellar cases we had been considering, but rather tumors of the meningioma (dural endothelioma) group that were deviating toward an angioblastic structure; and we were aware that an attempt to explain our conception of this matter would lead us too far from the primary object of the original monograph, from which this paper is only an offshoot.

By the term *angioblastic meningioma* we do not mean meningomas* that merely happen to be highly vascular in the sense that the term angioglioma is sometimes used for a highly vascular glioma. What

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*The term meningioma was introduced by one of us (Cushing: 1922)[9] primarily to elbow out of use the term "dural endothelioma," which was regarded as a misnomer, since the tumors are neither dural in origin nor strictly speaking endothelial. Many qualifying terms (fibroma, psammoma, etc.) had been given to these growths supposedly of dural origin, and it seemed desirable to employ a more embracing term which would connote the particular and familiar type of growth that arises from the functionally active cells of the arachnoid (meningocytes) and which should be sharply distinguished from the true blood-vessel tumors of the brain that are often sufficiently cellular in type to justify the term hemangio-endothelioma.

The term leptomeningioma has been suggested by Learmonth[6] (1927) as more specifically denoting the source of the tumor, but as this is a longer word and since the pachymeninx does not give rise to tumors, it seems hardly necessary. Mallory,[10] who for some years regarded these tumors as being endotheliomas, finally, as he states, chanced to find fibrillae in one specimen and consequently changed his views regarding them and has since called them "arachnoid fibroblastomas." To this term Penfield[23] in a recent article has given his support.

we do mean is that a meningeal tumor which possesses the unmistakable naked-eye appearance of the usual and familiar type of one of these lesions may prove histologically to have the same architectural features and reticular network that is possessed by the hemangioblastomas which originate within the brain itself, more frequently, if not exclusively, in the cerebellum.

We do not propose to enter here into a full discussion of the histogenesis of the meningiomas and of their transformations or variations in type, for this is a subject by itself. It must suffice to say of our series (to March 1, 1928) of 185 intracranial meningiomas which have been carefully restudied: (1) that about 90 per cent of them are of the pure and well recognized mesotheliomatous type; (2) that of the remainder, a few show definite fibroblastic characteristics (archnoid fibroblastoma of Mallory and Penfield), an occasional tumor having become almost wholly fibromatous; (3) that a few have definite sarcomatous tendencies; and (4) that the three cases herein recorded show the unmistakable histologic characteristics of a hemangioblastoma.

Though the intracranial meningiomas, as it is well known, far more commonly arise from the cerebral than from the cerebellar envelops [the proportion in our series being 172 (92.9 per cent) to 13 (7.1 per cent)], there is no inherent reason why the tumors involving the hindbrain should not show comparable histologic deviations from the usual type.* It may be said, however, that there is a tendency on the part of these meningeal tumors arising from one or another locus to show similar gross and histologic peculiarities in growth; and as will be observed, the three tumors herein reported as having an angioblastic structure arose from the supratentorial surface, this being a comparatively infrequent point of origin for meningiomas of any sort.

To these three cerebral cases we will now turn our attention. It will be seen that all three were solid, encapsulated lesions which showed no tendency to form cysts and in this respect were unlike the more common cerebellar hemangiomas. All three of them consequently at the time of the primary operation were regarded, on the basis of their gross appearance, merely as unusually vascular meningiomas, an opinion which was supported by the original pathologic reports on the tissues. In none of the three cases was a primary complete extirpation successful, and the recurrent growth ultimately attained a huge size.

CASE REPORTS

The tumor in the first of the cases, the report of which follows, is one that in all probability at the present day with a more exact

*In our series of twenty meningiomas of the spinal cord, we have found one of the cases re-examined to be a typically angioblastomatous lesion, so that the tumors in question are therefore not restricted to the cerebral meninges.

localizing diagnosis, a better exposure, and with electrosurgical methods of enucleation, might have been wholly and safely removed at a primary session. The patient was the wife of a physician, and the fact that she was made comfortable for a period of three years alone serves to lessen our retrospective regrets over the outcome of the case.

CASE 1.—*Symptoms of left cerebral tumor. Osteoplastic exploration and decompression without disclosing lesion. Partial extirpation of massive occipital lobe meningioma at second operation: pathologic diagnosis—vascular glioma or endothelioma (?). A third operation a year later for recurrence of symptoms: pathologic diagnosis "endothelial sarcoma." A fourth operation after another two years with fatality. Autopsy: ultimate diagnosis—angioblastic meningioma.*

June 3, 1913.—Admission of Mrs. C., aged 44, referred by Dr. James H. Glass of Utica, N. Y., complaining of headache, failing vision and unsteady gait.

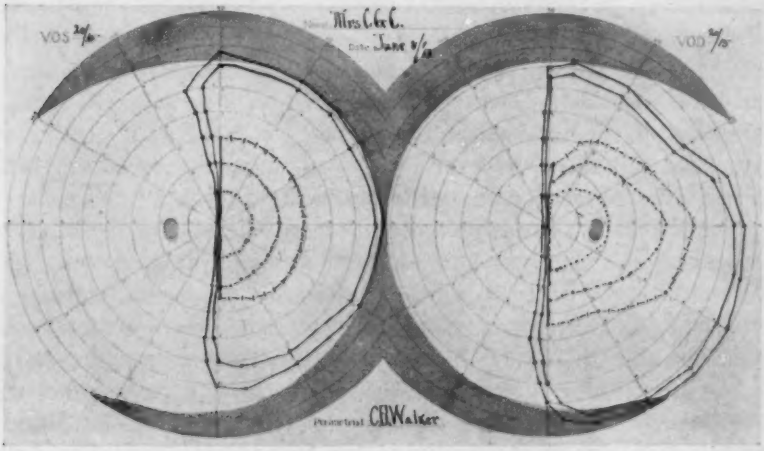


Fig. 1 (case 1).—Fields of vision on admission to hospital on June 8, 1913.

Anamnesis.—She had always been well until about three years ago, when she began having periodic right suboccipital headaches on first arising. These morning headaches have recently become much worse and have occasionally been severe but have never been associated with vomiting. Even when free from headache, she latterly has had a tight, heavy feeling over the entire head, with more or less constant soreness of the right suboccipital muscles.

Seven months ago, in November, 1912, she noticed some haziness of vision, but it was not until February, 1913, that she became aware that she could not see objects on her left side. For six or eight weeks her gait has been very unsteady. She has felt dizzy at times and occasionally hears a noise like a distant steam engine, chiefly in the right ear.

Examination.—There was found a bilateral choked disk of 2.5 to 3 diopters; a left homonymous hemianopsia (fig. 1) with vertical meridian bisecting the macula; a hemiopic papillary reaction from the blind fields; inequality of the pupils, the left larger than the right. There was possibly a slight hypesthesia of the left face and hand. The Romberg sign was positive, and she tended consistently to fall to the left. There was a sustained nystagmus on looking to

the left; stooping produced marked vertigo. Suboccipital tenderness was marked on the right. The x-ray showed a slightly enlarged sella turcica.

The localizing diagnosis depended wholly on the homonymous hemianopsia in the absence of which, from blindness or other cause, the symptoms would have been strongly suggestive of a cerebellar lesion.

Operation I, June 10, 1913.—Under ether anesthesia a left, posteriorly placed, osteoplastic flap was turned down, and, owing to the great tension, a subtemporal defect was immediately made. As there were no surface indications of a lesion and as puncture of the hemisphere led to bleeding, the flap was replaced and the wound closed, the impression being that there was a large deep-seated occipital glioma.

Interval Notes.—She made an excellent surgical recovery with complete subsidence of the choked disk and relief of her discomforts. At the time of her discharge, June 30, 1913, though her gait was still slightly unsteady, her condition was in all respects much improved. In subsequent letters, however, she complained that something was wrong with her left hand; that she often "lost it." Because of a gradual increase in these left-sided sensory disturbances associated with a return of headaches, she re-entered the hospital three months later.

Second Admission, Sept. 15, 1913.—The subtemporal decompression at this time was found to be somewhat bulging. There was a return of the choked disks which measured from 1 to 1.5 diopters. As before, the left pupil was larger than the right, there were nystagmoid movements and a sharply cut left homonymous hemianopsia. In addition, there was a marked hypesthesia to pain, touch and temperature with a disturbance of postural sense over the entire left side, so that she was wholly unable to recognize objects in the left hand. She complained of a peculiar sensation of soreness to pressure on the affected side and the deep reflexes were slightly increased.

Operation II, Sept. 18, 1913.—Under ether anesthesia, the boneflap was re-elevated, exposing a dura under great tension; the cerebral gyri were markedly flattened and dry. An incision was made through the cortex in the occipital region and at a depth of about 2 cm., the smooth surface of a large, reddish, vascular tumor was encountered. The flap was most awkwardly placed for a satisfactory exposure of the lesion, and in the effort to uncover it, some bleeding was produced which made it necessary to enucleate the lesion as well as possible by finger-dissection. A mass about the size of a hen's egg was removed. It was evident that the extirpation was incomplete and that fragments of the tumor, which appeared to be attached to the tentorium and possibly to the lateral sinus, were left behind. Bleeding was finally checked by packing temporarily with cotton wet in hot saline. The boneflap had to be sacrificed and the scalp alone was closed over the protruding brain.

First Pathologic Report.—The portion of the tumor that had been removed was submitted to the pathologic laboratory under the assumption that it was a "dural endothelioma," but Professor Councilman after a careful study came to the conclusion, on the basis of what he took to be a "few thick neuroglia fibrils," that it must be a glioma. He noted, however, that it was exceedingly vascular and cellular for a glioma; also that in view of the abundant nuclear figures the tumor was one of rapid growth.

Interval Notes.—The patient made a good recovery from the operation though healing was complicated by a cerebrospinal fluid fistula; a small fungus developed in the anterior portion of the wound but this defect was repaired

on October 6th. The choked disks again subsided; the headaches were relieved; the hypesthesia of the left half of the body was much less pronounced, and she had regained in large part her stereognostic sense in the left hand by the time of her discharge on Oct. 19, 1913. The hemianopsia remained unaffected.

For the next several months she did surprisingly well, but by May, 1914, the disability of the left side had returned, and the leg had become affected so that her gait was shuffling. She was given a series of x-ray treatments, in spite of which she began to lose ground. Toward the end of May, there was a

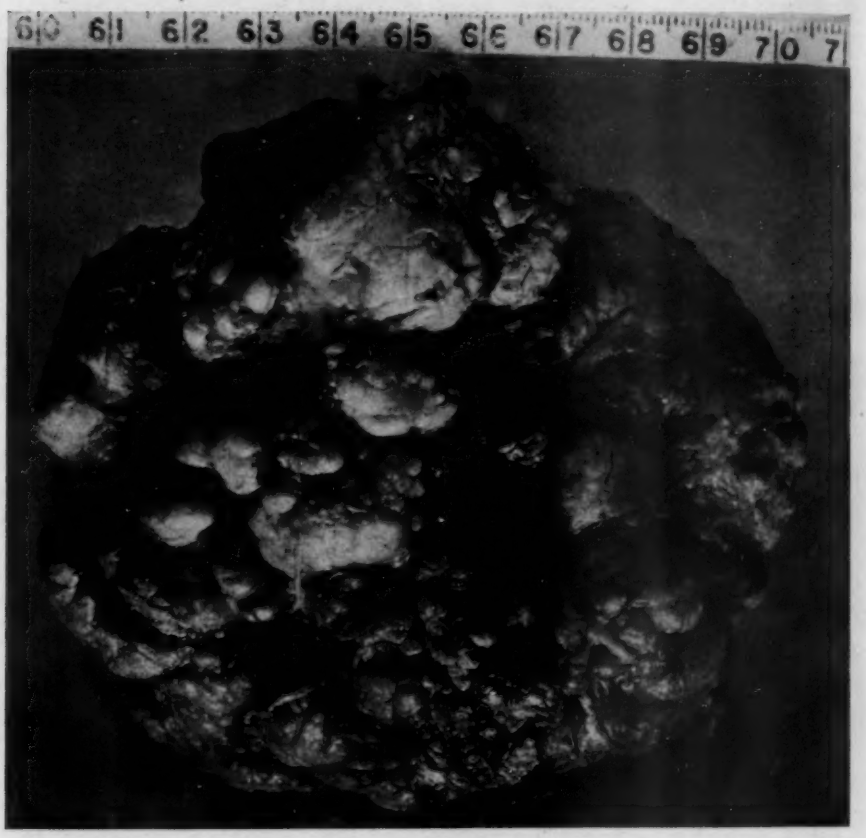


Fig. 2 (case 1).—Mass of tumor weighing 404.4 Gm. removed at third operation on Aug. 11, 1914 (natural size).

period of marked improvement, but subsequently this was lost and when headaches began to reappear she returned again to the hospital.

Third Admission, Aug. 4, 1914.—At this time, it was evident from the bulging area where the bone had been removed that the remaining portion of the tumor had greatly increased in size. The optic nerves showed secondary atrophy without measurable swelling. There was a left hemihypesthesia and left hemiparesis, left homonymous hemianopsia, marked incoordination of the left arm, hand and leg, probably due to astereognosis and loss of postural sense. All movements were possible but were slow and awkward.

Operation III, Aug. 11, 1914.—Again under ether, in the line of the old incision, the scalp was reopened. Beneath a thin layer of cortex was a huge recurrent enucleable tumor. The outer surface of the nodular growth was easily exposed, but finally bleeding was encountered and a hurried finger-enucleation was made necessary, a great mass of tumor weighing 404.4 Gm. (fig. 2) being removed. In the process, not only was the ventricle opened, but the growth was again broken off at its lower and posterior point of attachment. Bleeding was temporarily controlled by packing and finally by implantation of muscle taken from the patient's leg. A transfusion of 250 cc. of blood was made.

Fig. 3 (case 1).—Tumor mass weighing 220 Gm. as enucleated at the fourth operation (natural size).

Second Pathologic Report.—As the tumor was evidently noninfiltrating and as no neuroglial fibrils could again be identified, the previous diagnosis of glioma was altered to endothelioma—possibly an "endothelial sarcoma." Attention was called to the presence of large multinuclear cells resembling those seen in giant cell sarcomas of bone.

Interval Notes.—She had an uncomfortable convalescence. Wound healing was again complicated by a cerebrospinal fluid leak and some fever, but cultures showed no growth. The fistula finally closed spontaneously, and by Oct. 1, 1914, when she was discharged, her general condition was much improved, and

the area of the bone defect was soft and collapsed. The left homonymous hemianopsia and hemihypesthesia remained unaltered, but there was marked improvement in the use of her left arm and leg.

After her discharge, she did surprisingly well for nearly two years. She remained free from discomforts, gained weight, was able to get up and down stairs unassisted, and to conduct her household affairs. In June, 1915, she reported that she had been taking a mile-walk in spite of her lameness. In July, 1916, she wrote to say that the decompression was slightly less collopsed than it had been, but that her condition otherwise was practically unchanged and general health excellent. During the summer, however, the sunken decompression

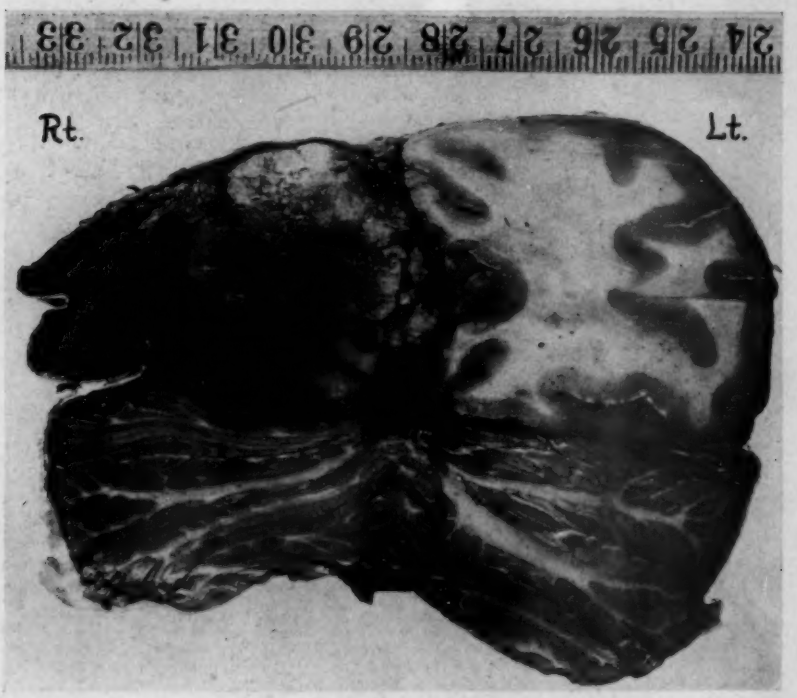


Fig. 4 (case 1).—Coronal section of brain through tips of occipital lobes showing part of tumor at tip of right occipital lobe not removed at operation.

continued to fill out, and by September, 1916, her headaches had returned, and she was readmitted to the hospital.

Fourth Admission, Sept. 27, 1916.—The previously sunken area was again protruding though not extremely tense. The local symptoms were otherwise about as noted at the time of her third admission two years before.

Operation IV, Sept. 29, 1916.—Under ether anesthesia, the original flap was again reflected, and a large recurrent growth was exposed occupying the region of the occipital lobe. It was very vascular. Between the lobes of the tumor were strands of tissue which made the growth more difficult to lay bare than on the previous occasion. There finally was considerable bleeding, which again necessitated a rapid finger-enucleation, and a great mass of tumor weighing

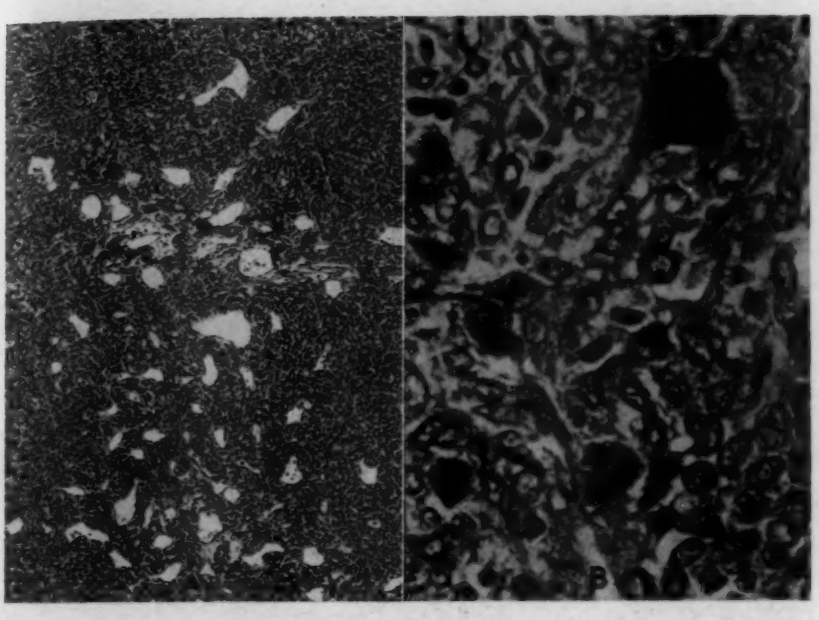


Fig. 5 (case 1).—*a*. Showing area resembling the structure of hemangioendotheliomas (H. and E.; ×80); *b*. two mitotic figures are seen and a giant cell (H. and E.; ×600).

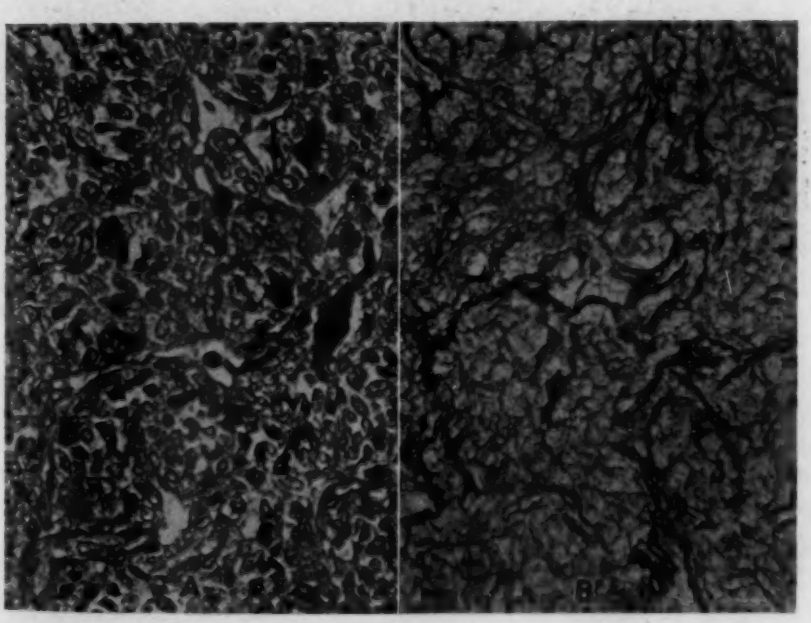


Fig. 6 (case 1).—Higher magnification of the tumor. *a*. Small capillary spaces and giant cells are seen (H. and E.; ×300); *b*. (Perdrau's method; ×300) showing the network of reticulin.

220 Gm. (fig. 3) was finally dislodged. Owing to the loss of blood during this procedure, she was again given a transfusion. The local bleeding was checked, as was thought, by placement of muscle and the wound was closed. She was very restless on recovery from the anesthetic, and died with symptoms of shock on the evening of the same day.

Necropsy.—The brain was removed after injection of formaldehyde through the carotid arteries. It showed a large defect in the occipital region of the right hemisphere. A section through the tip of the occipital lobe passed through a mass of intact tumor which still occupied this region (fig. 4). The growth was firmly attached to the posterior end of the falx, tentorium, and to the region of the sinus transversus. The cerebellum was flattened beneath a sagging tentorium, probably accounting for the cerebellar symptoms present during life. A coronal

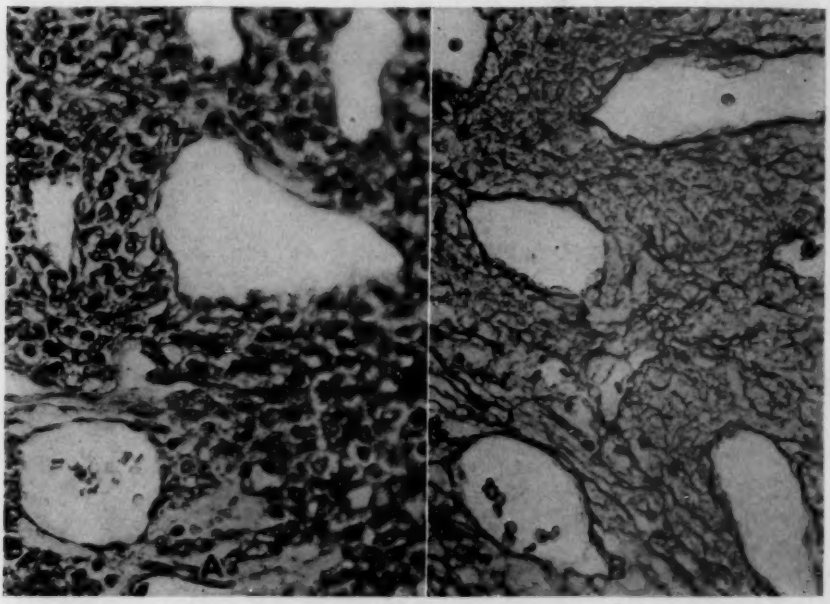


Fig. 7 (case 1).—*a.* Character of the neoplastic cells and of their nuclei is seen (H. and E.; × 300); *b.* network of reticulin formed by the cells (Perdrau's method, × 300).

section 1 cm. farther forward passed through a great cavity previously occupied by the growth. There had been bleeding into the ventricle, which had evidently been opened during the operation, and which was probably the cause of death. In the note concerning the microscopic observations on the tissue at the time attention was again called to the "sarcomatous appearance of the lesion" and to the numerous mitoses.

Microscopic Description.—From all the specimens removed at the various operations and at necropsy, new sections were made and stained with aniline blue-orange G; hematoxylin-eosin; phosphotungstic acid-hematoxylin; van Gieson's stain; neutral ethyl violet-orange G; and by Perdrau's method.

The tumor, from whatever source sections were cut, had a fairly uniform structure which was more compact than in the cerebellar hemangioblastomas,

but the same open spaces were present (fig. 5*a*). The tissue was highly cellular, and the nuclei seemed to lie in the lightly staining strands of a loose syncytium of cytoplasm. Here and there the cytoplasm was condensed into a more heavily staining mass containing several nuclei, to form true tumor giant-cells (fig. 6*a*). Occasionally, also, this syncytium was the seat of a hyaline transformation. The nuclei were poor in chromatin. Mitoses were frequently seen. The nuclear membrane was heavily stained and usually irregular and angular (fig. 5*b*). In some areas could be seen large vascular cavities, most of which were empty, but some of them contained a few erythrocytes (fig. 7*a*). For the most part there was only a ramifying system of capillaries, often completely collapsed and usually empty. Strands of reticulin permeated the tumor in every direction and lay in most intimate contact with the neoplastic cells (figs. 6*b* and 7*b*). There was a little collagen around the larger blood vessels.

Pathologic Diagnosis.—Meningioma of angioblastic elements with tendency to sarcomatous transformation.

Comment.—This was one of the early cases in the tumor series which taught the senior author that a supratentorial lesion might be productive of cerebellar symptoms either from compression due to sagging of the tentorium or to herniation of the cerebrum through the incisura tentorii. Had blindness from secondary optic atrophy ensued before the patient came under observation, or had her condition been such as to preclude a perimetric examination, a cerebellar exploration might well enough have been undertaken. That a suboccipital operation under these circumstances may be attended with a high mortality has been pointed out in a recent article from this clinic by Francis Grant.

From our present-day standpoint, the operations in this case were mostly badly executed. The tumor though rapidly growing was encapsulated, and had the occipital lobe been exposed from behind, as it would be today under similar circumstances rather than from the side, a complete enucleation could doubtless have been successfully made even before electro-desiccation came to be employed for such a purpose. As matters stood, the mass enucleated at one session weighed over 400 Gm. and was one of the largest brain tumors removed in the hospital series.

It is obvious from the conflicting pathologic diagnoses made by Dr. Councilman, after a study of the tissue removed at the second and third operations in 1913 and 1914, that the tumor was an unusual one. In gross it had the characteristics of a meningioma; it evidently arose from the arachnoid and like all the meningiomas was densely adherent to the dura. Though first regarded in 1913 as a vascular glioma and a year later diagnosed as an endothelial sarcoma, it is a much more rapidly growing lesion than the usual meningeal tumor, and, to our belief, belongs unmistakably to the hemangioblastomas; the endothelial character of the neoplastic cells is shown by their tendency to form vascular spaces, and the reticulin-network strongly supports this view.

CASE 2.—*Symptoms of right temporal lobe tumor of eight months' duration. Exploratory craniotomy disclosing an encapsulated tumor considered to be inoperable because of its great vascularity. Verified "solid cellular angiosarcoma." Two years later attempted removal of tumor by electrosurgical methods with fatality. Autopsy.*

May 5, 1923.—Admission of Mrs. Helen T., aged 34, referred by Dr. G. S. Wickham of Lee, Mass., with the diagnosis of probable brain tumor and the complaints of headaches, petit mal and numbness of the right face.

Anamnesis.—Previously well, in September, 1922, eight months before admission, she began to have brief nocturnal "fainting spells" suggestive of petit mal. Similar attacks inaugurated by a gastric aura and a sinking feeling without loss of consciousness soon began to occur in the daytime and increased in frequency until four months ago when she was having up to eight attacks a day. She never lost consciousness during any of these spells.

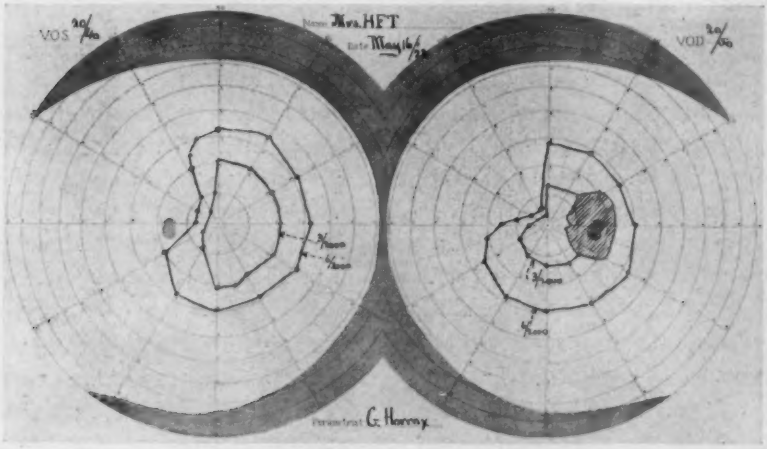


Fig. 8 (case 2).—Fields of vision (Screen Method) on first admission to hospital, May 16, 1923.

In December, 1922, she first noticed blurring of vision, which gradually increased until she could no longer see well enough to read print. For the past six weeks she had been having severe headaches, at first nocturnal but latterly continuing throughout the day. For six weeks also, she had noticed numbness of her right upper lip and maxillary region. For three weeks she had had intermittent diplopia and numbness of the fingers on both sides. For the last three or four days, there had been unsteadiness and a tendency to fall.

Examination.—The more definite objective observations were: a bilateral choked disk of 4 to 5 diopters with hemorrhages; limitation of upward conjugate movements of the eyes, and a left homonymous hemianopsia incomplete for the lower quadrants (fig. 8). There was also hypesthesia in all three divisions of the right trigeminal nerve; possible left facial weakness; and midline cerebellar signs, shown by suboccipital tenderness, slight nystagmus, a positive Romberg sign, difficulty in standing on either foot alone, poor resistance to pulsation backward or forward, and unsteadiness in gait. The x-ray showed evidence of increased intracranial tension with no localizing features.

The *diagnosis* in the absence of the perimetric observations would certainly have suggested a cerebellar lesion, but the left homonymous defect in the fields associated with the right trigeminal hypesthesia made a right temporal lobe lesion sufficiently definite to justify operation. However, as there was some difference of opinion, a ventriculogram was taken after the injection of air into the left ventricle, from which only 15 cc. of fluid was obtained. The films showed a normal left ventricle, the air being trapped and not passing over to the right. She was very much upset by this procedure, with greatly increased headaches, insomnia and vomiting, and it was a week before it seemed justifiable to operate.

Operation I, May 18, 1923.—A right-sided osteoplastic exploration with immediate subtemporal decompression was made. On incising the dura over the

Figure 9 Figure 10

Figs. 9-10 (case 2).—Patient on discharge, June 14, 1923, after first operation, showing moderate subtemporal protrusion.

temporal lobe, flattened convolutions were exposed with the sylvian vessels displaced upward. Palpation revealed nothing definite, but an incision was made through the cortex along the second temporal convolution, and at a depth of 2 cm. the smooth surface of what was taken to be a vascular endothelioma was exposed. Though the outer surface of the tumor was fairly well exposed, it lay in such a position that a piecemeal extirpation would have been necessitated if it were to be removed. Such excessive bleeding, however, was set up by the blunt incision through the capsule that it required the implantation of a piece of muscle taken from the patient's leg before it could be checked, and it was possible to remove only a small fragment of tissue for histologic verification of the lesion. Further procedures were abandoned; the flap was replaced and the wound closed.

Pathologic Report.—The tissue was reported to be a "hemangio-endothelioma" rather than the usual though vascular meningeal tumor that was anticipated.*

Interval Notes.—The patient made an excellent postoperative recovery, and she was discharged on June 4, 1923, with scarcely measurable elevation of the optic disks. Her headaches had been relieved; her cerebellar symptoms had practically disappeared; her gait and station were steady. She was still having occasional fainting attacks; the hemianopsia remained unaffected, and the subtemporal decompression was somewhat full (figs. 9 and 10).

The patient failed to report for nearly two years, when it was learned that after a period of improvement her former attacks, which had become more definitely uncinate in character, had returned. In spite of a series of deep x-ray treatments, her headaches had again reappeared in their former intensity, with

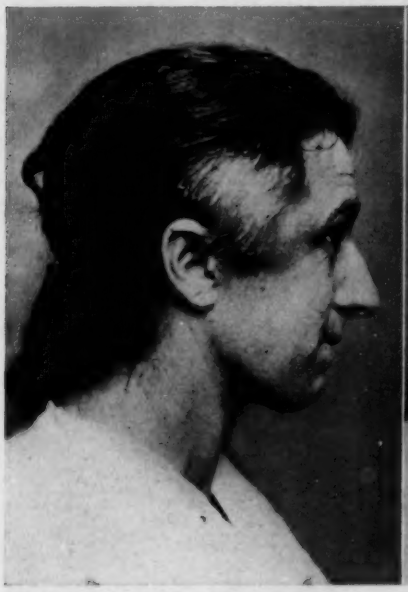


Figure 11

Figure 12

Figs. 11-12 (case 2).—Patient on readmission to hospital after two years' interval, showing increase in subtemporal protrusion.

bouts of vomiting, from which she was beginning to lose ground. Owing to the fact that at this time we had begun to have some encouraging results with the enucleation of vascular tumors by electrosurgical methods, she was encouraged to return to see what might be done.

Second Admission, Feb. 14, 1925.—The decompression at this time was found to be much larger than at the time of her discharge (figs. 11 and 12), though it was not particularly tense and there was no papilledema. The left homonymous hemianopsia had become complete; the hypesthesia in the right trigeminal area

* The patient happened to be shown at a meeting of the American Neurological Association on May 31, 1923, and the case at this stage was reported (Arch. Neurol. & Psychiat., 1923 x, 605-668, Case 20) as a meningioma (perithelioma).

had returned; there was slight weakness of the left face, arm and leg with exaggeration of the tendon reflexes; and unsteadiness of gait with tendency to deviate to the left. With many misgivings because of the proved vascular nature of the tumor a secondary operation was proposed. All preparations were made for a critical procedure.

Operation II, March 14, 1925.—As the tumor was thought to be probably of meningeal origin, in order to shut off the meningeal blood supply from the temporal fossa, the external carotid artery was primarily ligated, a step which considerably diminished the tension of the subtemporal protrusion. It was noted at the time that the common carotid and internal jugular were greatly enlarged.

Fig. 13 (case 2).—Tumor removed at second and fatal operation.

Under ether anesthesia, the original boneflap was then once more reflected, and the temporal lobe was well exposed. After brushing away the greatly thinned-out temporal cortex, a huge tumor the surface of which was covered by a network of tortuous vessels lay well exposed. The surface of the lesion was at first dehydrated and charred, but so soon as an attempt was made to excavate its central portion by using the Bovie loop, bleeding was excessive, difficult to control, and in such amounts as to preclude the further use of electrosurgical methods. It was obviously necessary to deliver the growth at whatever cost and subsequently to control bleeding at the base in the best fashion possible. The huge tumor (fig. 13), which weighed after removal 181 Gm., was slowly and gradually delivered. In this process, a portion of its capsule, adherent to the basal meninges near the midline of the skull, was torn off, and from this region there

was brisk bleeding which was finally controlled with difficulty. By this time the patient's blood pressure had fallen markedly, and her respirations had become impaired. Preparations for an immediate transfusion were made, but it was too late to save her life.

Postmortem Examination.—A postmortem examination was held. This disclosed a remaining thin shell of tumor which was firmly adherent to the tentorium; the cavity of the lateral sinus was invaded by the growth.

The Tumor.—Sections from the tissue removed at both operations were studied with hematoxylin and eosin; phosphotungstic acid-hematoxylin; aniline blue-acid fuchsin; and by Perdrau's method. They showed a similar structure. The growth, which had a definite capsule, was composed of elongated or ovoid endothelial cells provided with an almost imperceptible cytoplasm and irregular nuclei (fig. 14, *a*).

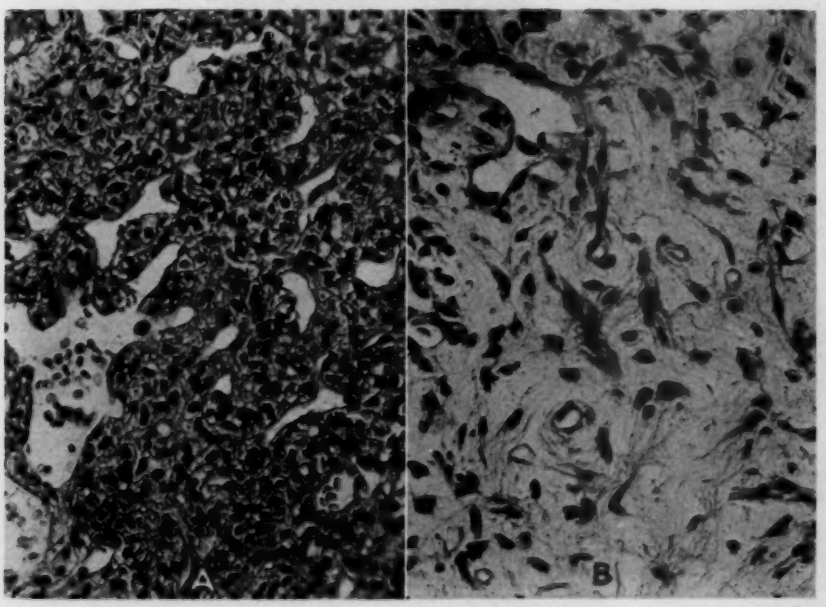


Fig. 14 (case 2).—*a*. From the fragment of tumor removed at the first operation, showing dilated capillary spaces between which lie the columns of endothelial cells (H. and E.; × 150), *b*. Area of undifferentiated mesenchymal tissue from tumor removed at second operation (H. and E.; × 300).

The nuclear membrane was heavy and angular; chromatin was scanty, and there were one or two prominent nucleoli. The cells were irregularly scattered between innumerable spaces which varied in size and configuration. These spaces did not always form a definite closed ring, and the neoplastic cells themselves, without the intervention of any wall, lined the cavities, which suggested the newly formed vessels in a spindle-cell sarcoma. In certain areas the nuclei were widely separated by a delicate, structureless material in which no fibrillae were present. These areas resembled myxomatous tissue (fig. 14, *b*). Other portions of the tumor more closely resembled a sarcoma (fig. 15, *a*). No veins or arteries were seen. Many cells were vacuolated; the vacuoles originally contained fat, as was proved by Herxheimer's method. Areas of cystic degeneration were present, owing to

hyaline and granular degeneration of the tumor cells. Between the cells was laid down an abundant network of reticulin (fig. 15, *b*). Mitotic figures were rarely seen.

The tumor, which had the structure of a hemangio-endothelioma, is best described as a hemangioblastic meningioma.

Comment.—From a clinical standpoint, the case is interesting in connection with the preceding one, in that a sufficiently definite cerebellar syndrome was present possibly to have justified a suboccipital exploration had not the homonymous hemianopsia been disclosed. It is, of course, well known that a temporal lobe tumor may in its effects closely simulate a subtentorial lesion.

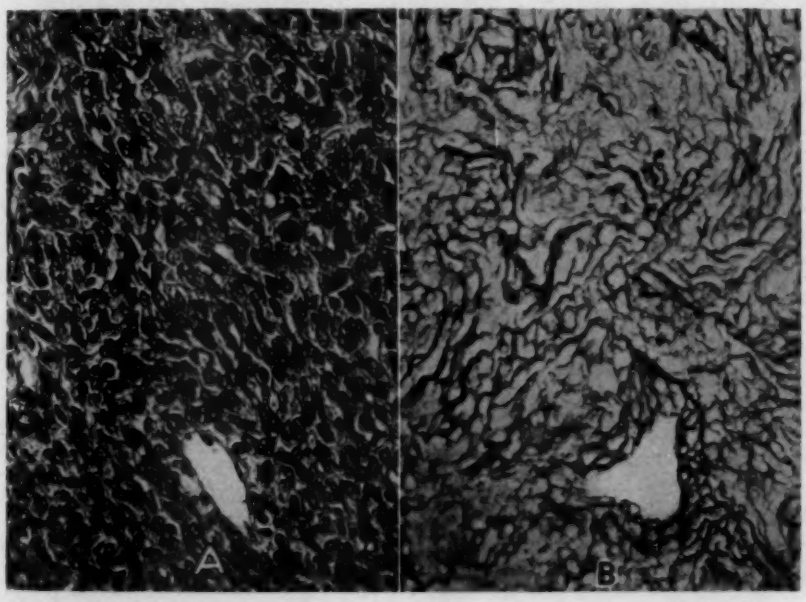


Fig. 15 (case 2).—Sections from the tumor removed at the second operation; *a.* showing an area with sarcomatous structure (H. and E.; × 300); *b.* network of reticulin in the same area (Perdrau's method; × 300).

Here again was an enormous tumor occupying a relatively silent area of the right hemisphere, and, apart from the general pressure effects, causing surprisingly few serious symptoms in spite of the extreme cerebral dislocation. That it was a desperate throw to undertake the removal of a growth of this size and character was fully realized, but the unfortunate woman had already exceeded the period when the decompression alone could save her for a life worth living. Whether our present greater experience with electrosurgical methods could have helped us to see the procedure through with less loss of blood is perhaps doubtful; but there is no question of there having been a technical error

in not having the donor's blood ready to be introduced before the tumor was delivered rather than to run the risk of unnecessary delay afterward.*

The tumor in this case, of all three, bears the closest microscopic resemblance to the cerebellar hemangioblastomas which we have elsewhere described, it being almost identical, for example, with the solid midcerebellar lesion in case 16 of our earlier report.[4]

We now come to the last and most remarkable of these three tumors. It is the only case in which the growth became highly malignant, as do some of the angioblastic lesions in other parts of the body, and it is the only case in which it became aneurysmal in character. It consequently serves to recall the subject that engaged our attention in our monograph when considering the angiomatous malformations (angioma arteriale), for here was a solid tumor which clinically became associated with a loud systolic bruit. The detailed story of our ineffective efforts to aid this courageous young woman in the course of her five hospital admissions, her nine operations and 314 days of hospitalization would require a volume in itself. The essentials only need be given.

CASE 3.—*Cerebellar symptoms of sixteen months' duration. First and second-stage suboccipital explorations disclosing a highly vascular subtentorial tumor taken for a meningioma. Three subsequent attempts to re-expose tumor thwarted by excessive bleeding. Aneurysmal characteristics of tumor first recognized two years later when occipital lobe symptoms had appeared. Three-stage occipital decompression with tumor verification as "perithelioma." Four years' course from onset to death. Autopsy. Huge solid malignant hemangiosarcoma occluding lateral and longitudinal sinuses.*

Oct. 11, 1921: Admission of Miss Julia M., aged 30, referred by Dr. E. W. Mulligan of Rochester, N. Y., because of cerebellar symptoms with choked disks.

Anamnesis.—Until the onset of her present illness, the patient had enjoyed unusually good health. Her symptoms occurred in the following sequence:

(1) On June, 1920, after holding her head back while swimming, she experienced a sudden severe pain in the back of her neck. In October, 1920, after holding her head back while dancing, she had a second and more persistent attack of the same kind. During the next few months, periodic suboccipital headaches which would wear away after a short rest have been produced by such simple acts as straining at stool. Since March, 1921, she had usually awakened with a severe headache which would subside after taking acetylsalicylic acid. The headaches were associated with a feeling of stiffness and soreness on turning the head.

(2) For seven months, since March, 1921, she had been conscious of an impaired sense of equilibrium causing unsteadiness. (3) Since June, 1921, she had gastro-intestinal symptoms with indigestion, nausea and occasional vomit-

* In the examination of this patient, no note was made of auscultation of the head. Since this paper was prepared, a precisely similar tumor in the same situation has been encountered in which an audible bruit was detected before the operation.

ing. (4) In July and August, she had been disturbed by tinnitus—a whirring sound referred to the right ear. (5). Since August, there has been some dysphagia, the swallowing of liquids often producing coughing. (6) Blurring of vision in the left eye had been noticed of late, ascribed to a retinal hemorrhage; and more recently there have been periods of temporary amaurosis on suddenly arising.

She had been treated meanwhile for a variety of ailments; myopia and astigmatism; nervous indigestion; hyperacidity; intestinal toxemia; albuminuric retinitis, etc.

Examination.—This revealed a bilateral choked disk of 2.5 diopters on the right, where there was considerable new tissue, and of 4 diopters on the left, where there were hemorrhages and exudates suggesting an albumnuric retinitis. The pupils were much dilated and reacted poorly to light. The fields of vision were normal; visual acuity was slightly reduced. Such as they were, the localizing symptoms all pointed to the cerebellum, though on only one occasion by one observer were a few nystagmoid jerks noted.

The *objective observations* were: suboccipital tenderness and discomfort on forced flexion of the neck; a positive Romberg sign with tendency to fall backward; considerable unsteadiness in gait with reeling to the left; some hypotonia, more marked in the lower extremities than in the upper; slight dysmetria apparent on movements of the right foot. There was no definite asynergia or ataxia of the individual extremities, though one observer thought the finger-nose test on the right brought out some ataxia. The deep reflexes were elicited with difficulty, and the abdominal reflexes were not obtainable.

Diagnosis.—The symptoms, though not very conclusive, were thought sufficient to justify a suboccipital exploration. A decompressive procedure of some sort was urgently needed to save vision. There is no record at this time of any auscultation of the head.

Operation I, Oct. 17, 1921.—Under ether anesthesia, the attempt to make the usual bilateral exposure of the subocciptal region met with an unexpected vascularity of scalp, muscle and bone. The skull was found to be perforated in many places by large sinusoidal openings from which venous blood spurted; these openings were controlled with difficulty with wax. An attempt to puncture the left ventricle to reduce tension was unavailing; on the right, the ventricle was finally located on the third tap, and about 20 cc. of fluid under great tension was secured. Attempts to complete the suboccipital bone defect led to such bleeding that, owing to the patient's condition, the operation was abandoned for a second stage.

Interval Notes.—Following this unsatisfactory procedure, she passed an extremely uncomfortable week, and not until nine days had passed was it thought safe to resume the exploration.

Operation II, Oct. 26, 1921.—Under ether anesthesia, the flaps were reflected a second time, but in the process of completing the bony opening excessive bleeding again occurred from bone as well as from the surface of the exposed dura. An area of especial vascularity of the dura lay below and to the right of the torcular. Here the tense membrane seemed somewhat roughened, and it was surmised that there would be an underlying meningioma. On opening and reflecting the dura, a bulging cerebellum with marked foraminal herniation was exposed. In the situation shown in figure 16, there was brought to view the lower pole of a smoothly encapsulated though highly vascular tumor evidently plastered against the tentorium and lateral sinus. Owing to the loss of blood, the patient's condition at this juncture became so critical that the procedure had to be hurriedly concluded.

After implantation of muscle taken early in the operation from the patient's leg, the wound was again closed.

Interval Note.—She had a very close call from this operation which was followed by a period of marked secondary anemia (hemoglobin, 30 per cent; erythrocytes, 1,632,000). She, however, experienced considerable subjective relief from the effects of the decompression, and, all things considered, the convalescence from this session was less trying than that from the preceding one. Before closure of the wound, a layer of gutta percha tissue had been implanted over the surface of the tumor and cerebellum to prevent the formation of adhesions,

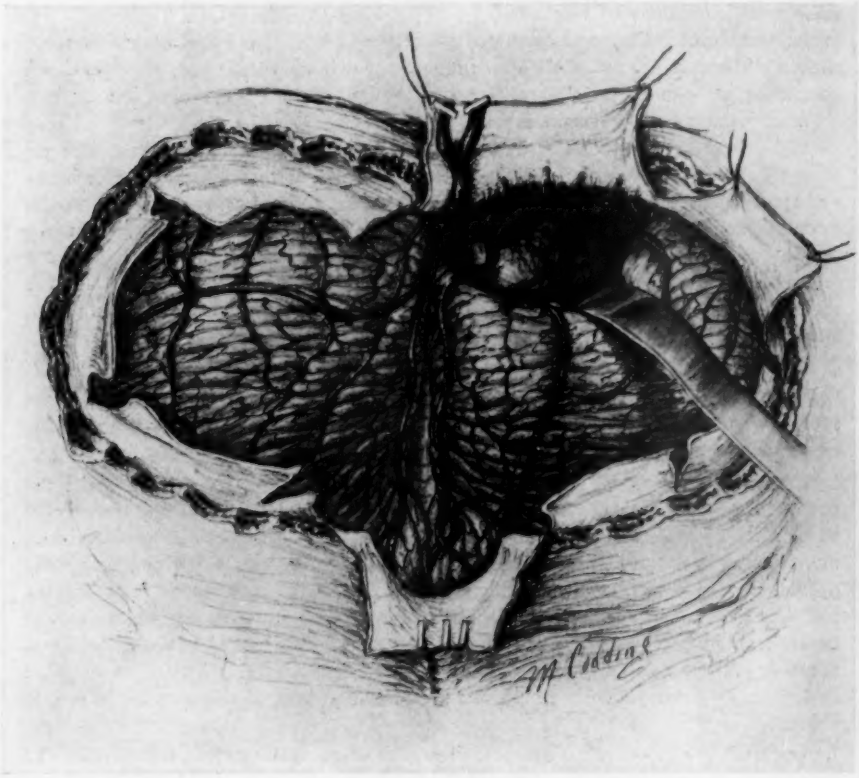


Fig. 16 (case 3).—Sketch of tumor as exposed on second operation, Oct. 26, 1921.

with the hope of thereby facilitating the re-exposure of the field should it be possible to operate again. After a three weeks' interval, a third attempt was made.

Operation III, Nov. 15, 1921.—On this occasion, under procaine anesthesia, it was found to be impossible even to reflect the flaps, owing to the excessive oozing of thin, watery blood from large sinusoidal spaces that were encountered in the recent scar tissue. Her blood pressure promptly dropped so that it could no longer be registered; she became pulseless, and had it not been for an immediate transfusion of 500 cc. of blood from a donor who had been prepared, the story would probably have ended then and there.

Interval Note.—Owing to the hurried wound closure with deep through-and-through sutures which were too tightly tied, there was a superficial slough on the right side of the crossbow incision. This, with her extreme anemia from which she picked up very slowly, necessitated a long delay, and six weeks passed before it was though safe to make another attempt. By this time her hemoglobin had slowly risen to 65 per cent, and her erythrocytes to about 4,000,000.

Operation IV, Dec. 27, 1921.—The attempt to reopen the wound met with no better success than at the third session. Formidable bleeding, which could neither be controlled by clamps nor by pressure, was set up by the primary incision in the

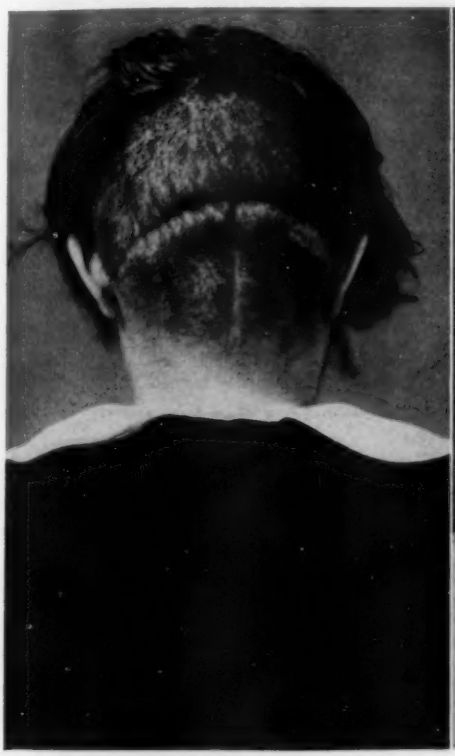


Figure 17

Figure 18

Figs. 17-18 (case 3).—Field of operation (left) Jan. 10, 1922, on patient's discharge after the fourth attempted cerebellar operation; (right) Feb. 28, 1924, on her discharge after three further successive and hazardous attempts to deal with the occipital extension of the tumor followed by radiotherapy.

line of the old scar. To press matters further was obviously foolhardy. The wound was again rapidly closed by through-and-through sutures, for the usual detailed closure by layers would have been impossible.

Interval Notes.—Again, owing to the manner of closure, there was imperfect superficial wound healing; but she picked up rapidly from this last operation and fortunately by this time, from the effects of the decompression brought about at

the second session, the choked disks had gradually subsided, leaving a moderate secondary atrophy but with preservation of useful reading vision. The decompression, however, had led to some increase in her cerebellar symptomatology, definite nystagmus, dysarthria and an increase in the ataxia of the right side having been added to her previous syndrome. She was discharged (fig. 17) Jan. 11, 1922.

Interval Notes.—The patient was far less disheartened than we were by our surgical inadequacy, and after two months in the South, where she gained weight and recovered wholly from her anemia, she was readmitted at her own request because of the recent return of her former nausea.

Second Admission, March 28, 1922.—Aside from the returning nausea of which she complained, the examination at this time showed a marked objective improvement in all respects. The blood picture was normal. There was no swelling of the optic disks; the secondary atrophy seemed less apparent; she had retained practically normal acuity. [The fields of vision were not charted; there was no note of auscultation of the skull.] She still had considerable dysarthria, but her former cerebellar symptoms had largely disappeared. Gait and station were normal: no nystagmus, no Romberg sign and no ataxia were present. It was felt that conditions justified a re-exploration.

Operation V, March 31, 1922.—The attempt to reopen the wound met with even more serious bleeding than at the two preceding sessions. The scar was filled with huge dilated sinuses which were controlled only by the temporary placement of strips of pectoral muscle secured from a breast amputation on another patient. An attempt again to puncture the left lateral ventricle was followed by serious bleeding from the needle at a depth of 2 cm. The operation was concluded.

Interval Notes.—She recovered without incident from this disconcerting procedure. With the faint hope that the worst of the unaccountable bleeding might have been overcome and that it might be possible as at the first operation to get into a dilated right ventricle and so relieve what was supposed to be bleeding largely from venous stasis, another trial was made.

Operation VI, April 6, 1922.—Again under ether anesthesia, the incisions so far as they had been remade at the preceding stages were this time opened without loss of blood, even after removal of the strips of implanted muscle. A puncture of the right ventricle was made without incident, and a large amount of fluid under no especial tension was secured. It was hoped that it might be possible to complete the reflection of the flaps and that our troubles from wound bleeding would be largely over if it were only possible to get down to the layer of implanted gutta percha tissue. But so soon as this was attempted, new sinusoidal spaces were opened from which blood literally gushed as from an accidentally opened jugular vein. Fortunately, a large amount of fresh muscle was at hand with strips of which these openings in the scar tissue were plugged. Repeated attempts were made by retraction and compression to make advances in the exposure in one place or another, but at each attempt we were baffled by renewed and profuse bleeding. In despair, the procedure was abandoned as hopeless, and the wound reclosed without even an attempt to remove the implanted muscle.

Interval Notes.—She made a surprisingly good recovery from this desperate procedure. The wound healing was perfect. Her condition remained unaltered, the persistent nausea being her sole complaint. Realizing by this time that we were dealing with a lesion that might possibly be something other than a meningioma, a series of deep x-ray treatments were instituted. She was discharged on April 22, 1922. During the next six months, she was given every

three weeks, by Dr. M. B. Palmer of Rochester, a series of x-ray treatments which were unquestionably beneficial.

Third Admission.—She re-entered the hospital for a period of observation from November 2 to 13, 1922. At this time she was found to be much improved in all respects. Apart from a recent heavy feeling in her head, she had few complaints. The nausea had disappeared, and the dysarthria was greatly improved. Though turning quickly caused some disequilibration, her gait was practically normal, and there was no nystagmus and a negative Romberg sign. The optic nerves had a fairly good color, were without swelling, and good reading vision was retained.

Interval Notes.—She subsequently passed the winter months in the Canal Zone, where she enjoyed the swimming and led a fairly active life. After her return, there were no untoward symptoms until May, 1923, when she first noticed what appeared from her description to be visual hallucinations, and in the course of a few weeks it became evident that she did not see well to the left side. In

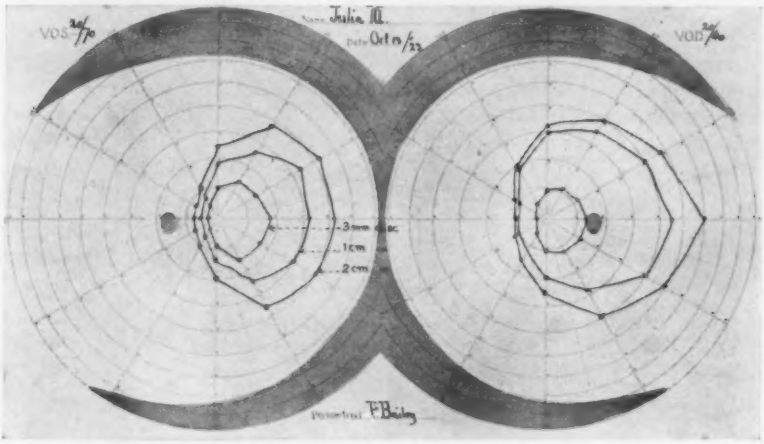


Fig. 19 (case 3).—Fields of vision on patient's fourth admission when an incomplete left homonymous hemianopsia was first observed.

August, 1923, she noticed a lump on the right occiput above the line of the old incision. Because of this, she re-entered the hospital.

Fourth Admission, Oct. 11, 1923.—The examination at this time showed practically no change in the very inconspicuous cerebellar symptomatology noted in November, 1922. There were, however, unmistakable evidences that the tumor had extended upward through the tentorium so as to involve the occipital lobe. There was a fairly complete (fig. 19) left homonymous hemianopsia, and through the patient's hair could be palpated, about at the site of the tumor that had been previously exposed, a firm immovable tumor mass. About 4 cm. higher up and to the outer side, another unmistakable nodule could be felt at the point where the skull had been perforated for the purpose of tapping the right ventricle. The x-ray showed a marked porosity of the occipital bone in this region, which suggested to Dr. Sosman a "luetic osteitis."

At about this time, we had had under observation a patient with a large meningioma which lay both above and below the tentorium. Assuming that Miss M. had a lesion of the same kind, it was felt that in view of the comparative

quiescence of the cerebellar symptoms, an occipital decompression, if one could be safely carried out, was indicated to forestall if possible a further advance of her symptoms.

On shaving the patient's head in preparation for this operation, there was disclosed *an amazing condition of the occipital scalp resembling a cirsoid aneurysm,* with highly dilated lakes of blood overlying the region of the old wound. On listening to the region for the first time with a stethoscope, *a systolic bruit* was heard of which the patient was unaware. It was most intense in the region of the right mastoid, where a greatly enlarged artery was palpable, but it was heard

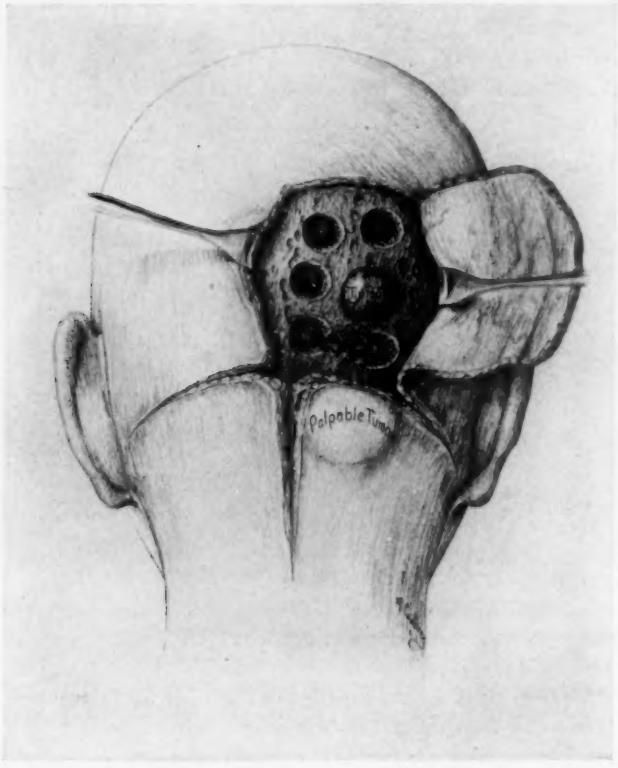


Fig. 20 (case 3).—Sketch of field of first occipital operation as exposed Nov. 8, 1923, when the attempt was made to surround the central area of tumor by perforations.

also up over the back of the head. Carotid compression was found largely though not completely to subdue the bruit.

Operation VII, Nov. 8, 1923.—Under ether anesthesia, the right external carotid was ligated. The patient was then placed face down on the cerebellar table and an occipital flap was outlined, the old incision serving as its lower leg. It was an exceedingly bloody procedure, in spite of the carotid ligation, but it was finally possible to expose the greatly roughened and highly vascular bone in the center of which, as shown in the accompanying sketch, there was a nodule of

tumor projecting through the bone at the site of the former ventricular puncture, the original opening having become greatly enlarged from pressure absorption.

It was determined if possible to remove the bone from over the surface of the lesion by encircling the central protrusion with a series of perforations which were subseuently to be connected. Five of these perforations were made, and the lower two, as shown in the operative sketch (fig. 20), were united. Bleeding meanwhile was excessive and controlled with difficulty with wax and muscle implants. Finally, when her pressure began seriously to fall off, the wound was closed, and she was re-fused by Dr. Loyal Davis with 600 cc. of the mixture (containing 2,800,000 red cells per cm. and showing 50 per cent hemoglobin) of her own blood and saline solution, which had been collected by suction from the wound during the course of the nearly four-hour procedure.

Interval Notes.—She made so excellent a recovery from this operation that we were encouraged to continue in the attempt fully to uncover the occipital tumor.

Operation VIII, Nov. 14, 1923.—At this session, again under ether anesthesia, it was possible to complete the encirclement of the central tumor by perforations and to connect them. When this had been accomplished, the imprisoned tumor promptly bulged into the wound, though the dura was still intact. A few of the encircling fragments of bone adjacent to the central protrusion were disloged, but this led to bleeding which was with difficulty checked by implantation of fresh muscle which was at hand. The wound was covered with a layer of gutta percha tissue and the flap replaced. No transfusion was performed.

Interval Notes.—Following this operation, she showed a moderate secondary anemia, and two weeks elapsed before it was thought safe to attempt any further procedure. She meanwhile became conscious of the bruit which had returned in its former intensity over the occipital area.

Operation IX, Dec. 1, 1923.—At this session, bleeding from sinusoidal spaces in the cicatrix presented the same difficulties that had been met with in the second, third and fourth operations. As no muscle was at hand, it had to be taken for a second time from the patient's leg; it was much needed before the end. The flap was finally reflected from the tumor, the protrusion of which had evidently increased in the intervening two weeks. The dura was now for the first time incised close to the margins of the bone defect. The tumor promptly began to extrude, disclosing a smooth, encapsulated surface like that of a typical though very vascular meningioma. The growth dislodged itself to such an extent that reclosure of the flap would have been impossible. It consequently was necessary roughly to remove the presenting mass of the lesion including the original central nodule and its remaining encirclement of bone. In the absence of electrosurgical methods, this was done with a blunt scoop. This led to profuse bleeding, which was finally controlled with difficulty by the implantation of the available mass of muscle, over which the flap was then replaced and the wound closed.

Pathological Note.—The tissue that had been removed was submitted to the pathologic laboratory as having come from a presumptive meningioma. The diagnosis of an "atypical dural endothelioma" was returned. Our own diagnosis at the time was "parithelioma."

Interval Notes.—The patient was in such poor condition from loss of blood at the close of this desperate four-hour operation that blood was transfused, Dr. Lewis Foster volunteering for the purpose, as it was not thought advisable to use her own blood which was mixed with the débris and secretions of the healing wound. She made a fairly satisfactory operative recovery, but on this occasion we had the misfortune to have a mild wound infection, possibly not to be

wondered at in view of the bone wax, muscle from various sources, gutta percha tissue, etc., which had been buried at the several operations. Three sinuses formed from which bone wax and finally a few bone sequestrae were ultimately discharged. In consequence, the immediate and hoped for benefit of the operation was overshadowed by this long drawn out healing process, and it was not until weeks had elapsed that dressings were no longer necessary.

The clinical note by Dr. T. J. Putnam, who had been in charge of the case during these months, states at the time of her discharge, March 1, 1924, that: "She has gained weight, is comfortable, eats and sleeps well, and is 'feeling better than for several years.' She has no appreciable cerebellar symptoms; the flap of the recent wound over the tumor is only slightly elevated (fig. 18); a fragment

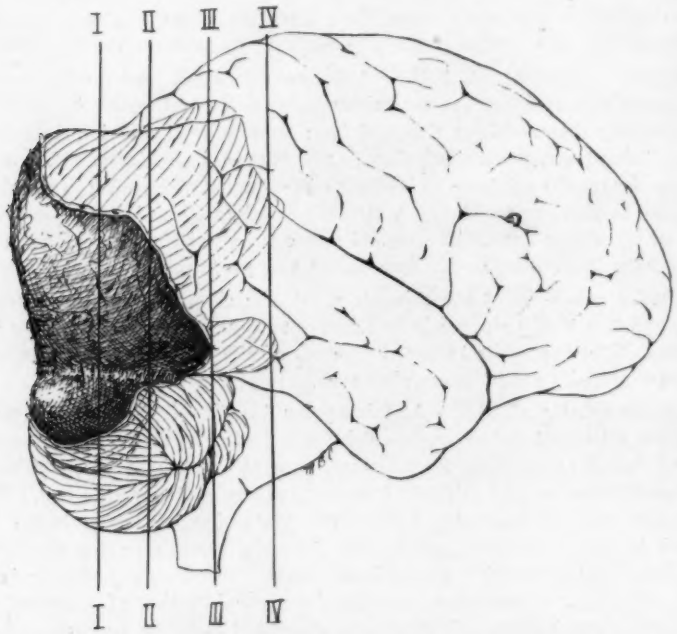


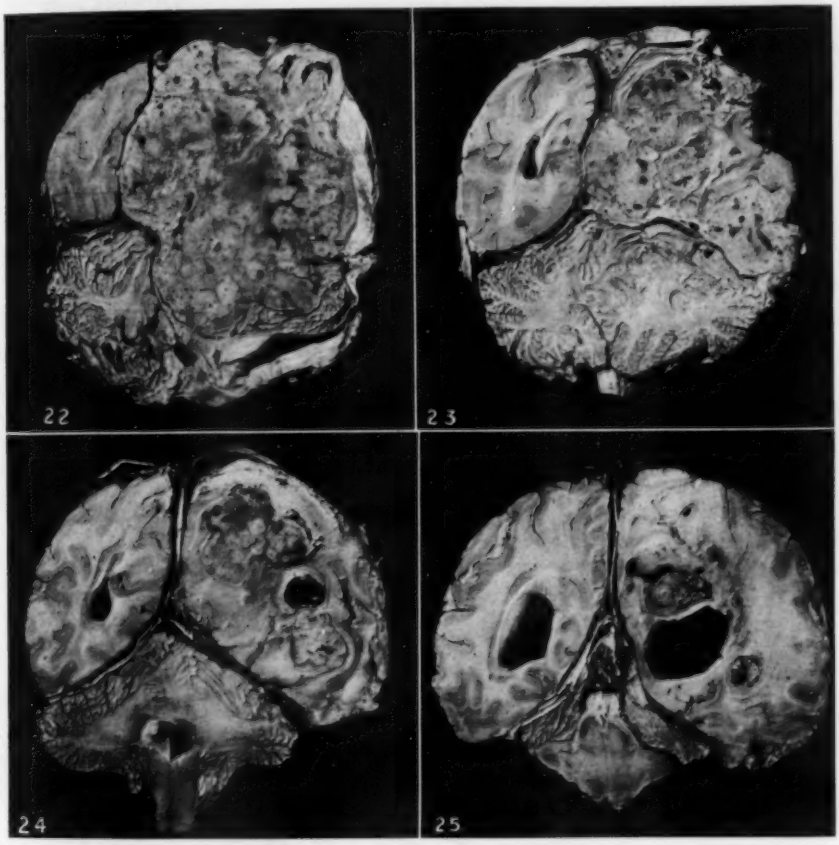
Fig. 21 (case 3).—Lateral aspect of brain showing diagramatically the extent of tumor and situation of sections described in text.

of necrosed bone which shows in the x-ray can still be detected at the bottom of one of the sinuses; the audible bruit persists over the right mastoid."

One disconcerting observation was made during this long period of convalescence; namely, that the left homonymous hemianopsia which had been incomplete (fig. 19) before the operation had gradually become complete in spite of the extensive decompression. This suggested either that the growth was progressing in spite of a second series of x-ray treatments that had been given, or that there might possibly be an abscess. We were prepared therefore in a measure for what happened.

Fifth Admission, March 25, 1924.—Some weeks after returning home, she began to complain of headaches; there was an occasional attack of nausea with vomiting; unsteadiness, from which she had been free for nearly two years, began again to be evident. She consequently was brought back to the hospital.

Previously always alert and responsive no matter how uncomfortable, she had become dull and apathetic; and her nutritional condition was poor. The region of the occipital decompression was full and strongly pulsating, and over it a systolic bruit was to be heard, though it was less pronounced than previously. There was some engorgement of the retinal veins, but no papilledema. The cerebellar symptoms in the absence of nystagmus were about as at the time of her first admission.



Figs. 22-25 (case 3).—Photograph of the four coronal sections (cf. figure 21) looking forward and showing tumor as described in text.

She gradually passed into a comatose state, and died quietly on April 10, 1924. The postmortem study was limited to an examination of the head. The brain was removed after carotid injection *in situ* with 10 per cent formaldehyde solution.

Pathologic Record.—Macroscopic Description: Externally the brain showed slight flattening of the convolutions. Occupying the posterior portion of the right cerebral and cerebellar hemispheres was an extensive tumor which was densely adherent to the overlying dura. It appeared to have incorporated and to have obliterated the lateral sinus and adjacent tentorium. Because of the accumulation of overlying scar tissue from various operations, it was difficult to determine its

exact boundaries, but it appeared to lie principally to the right of the falx cerebri and to extend below and through the tentorium. Over the cerebellum was a sheet of gutta percha tissue measuring 6 by 3 cm. implanted nearly three years ago, which lay without any accumulation of fluid between two glistening endothelial-lined surfaces.

A series of coronal sections were made at the levels shown and numbered in the diagram (fig. 21). Section I (fig. 22), made 2 cm. in front of the tip of the occipital poles, shows a huge tumor which had completely wiped out all landmarks on the right side of the brain except for a fringe of cerebrum above and of cerebellum, partly occupied by an arachnoid cyst, below. The falx had been pushed far to the left and what trace there was of the tentorium was deflected downward. There was no trace of the torcular or of the right lateral sinus. The cut surface of the tumor had a mottled appearance, resembling that of granite, and showed

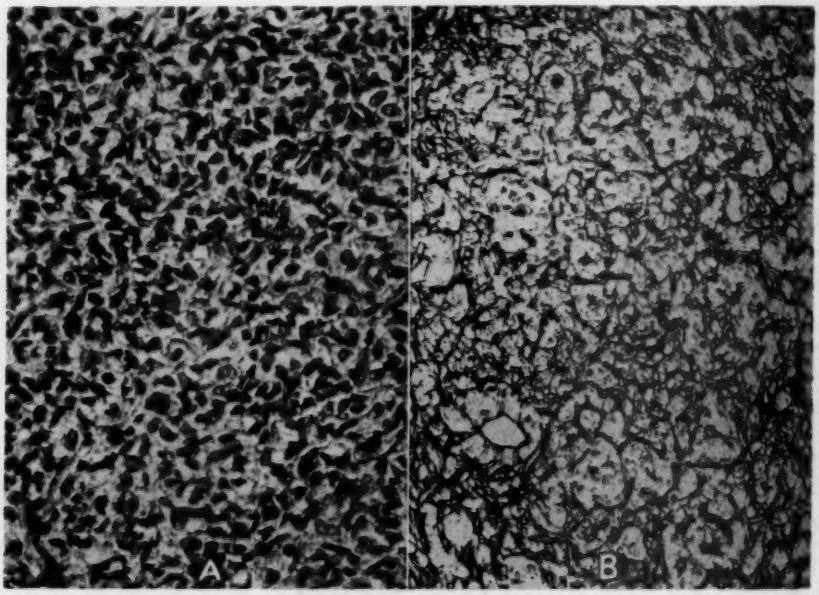


Fig. 26 (case 3).—Showing more solid portion of the tumor. *a*. The cells form innumerable capillary spaces (H. and E.; × 150); *b*, network of reticulin (Perdrau's method; × 150).

numerous small blood vessels scattered through it. It was sharply circumscribed from the cerebral tissue. Wherever it abutted on the pachymeninx, it was densely adherent to the membrane.

Section II (fig. 23), 2 cm. further forward, showed the tumor to be almost wholly above the tentorium. The growth was here everywhere covered by a thin layer of cortex except in the lower part of the field above the tentorium where it reached the surface. At the angle of falx and tentorium there was a large, somewhat distinct tumor nodule about 2 by 3 cm. in diameter, which extended across the midline, deformed the left occipital lobe, and produced marked dislocation of the sinus rectus. A small nodule of tumor was still visible on the cut surface of the cerebellum. The longitudinal sinus in this section was seen to be distended with tumor which was separated from the main growth by a compressed layer of cortex.

Section III (fig. 24) showed tumor still in the superior and also in the inferior longitudinal sinus, but there was no tumor at this level attached to the tentorium or to the falx cerebri. The section passed through the coarsely nodular anterior portion of the growth and disclosed a small abscess cavity. The lateral ventricle of the left hemisphere was somewhat dilated. The right ventricle did not appear.

Section IV (fig. 25) passed through the center of the pons about 1 cm. anterior to the section last described. It disclosed another, somewhat larger, abscess cavity around which were the several more anterior nodular projections of the tumor which contained small cystic areas filled with a gelatinous material. Tumor was still present occluding the longitudinal sinus.

Coronal sections taken more anteriorly merely showed asymetry of the two hemispheres, the right being much larger than the left; the midline displaced to the left; and the right ventricle flattened laterally.

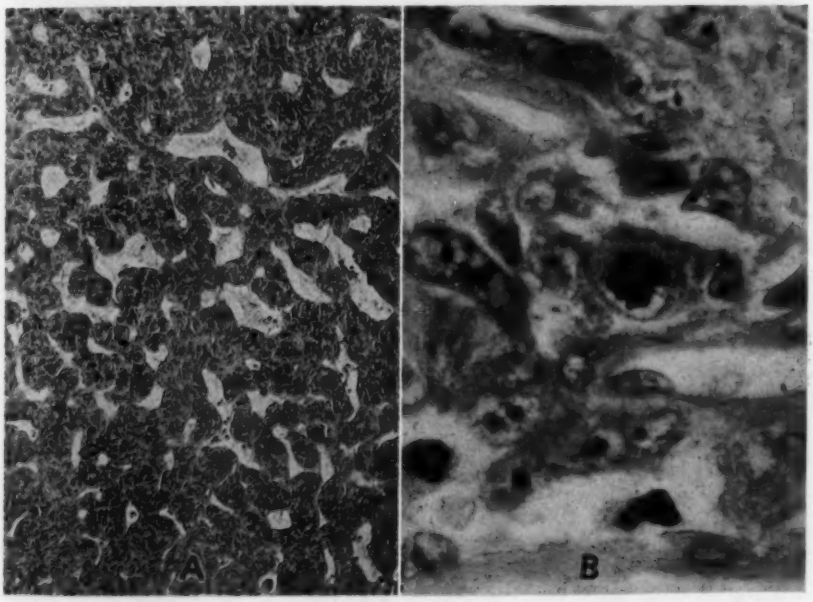


Fig. 27 (case 3).—*a*. Capillary spaces dilated, between which are columns of endothelial cells (methylene blue eosin; × 80). *b*. Note the capillary spaces and one mitotic figure (H. and E.; × 1,200).

Microscopic Examination: The same methods were used as in the previous cases. The tumor varied somewhat in structure in different regions. A part of the growth was composed of a more or less solid mass of cells (fig. 26, *a*) arranged in a disorderly way and embedded in a fine fibrillary network of reticulin (fig. 26, *b*). The cells varied in size from that of a small lymphocyte to that of a macrophage and larger. The scanty cytoplasm of the cells was homogeneous and pale red when stained with hematoxylin-eosin. The shape of the cells varied from irregularly round or kidney-shaped to oval or elongated, the last predominating. The cell boundary was usually sharply outlined. The nucleus contained numerous granules of chromatin and one or two nucleoli. Its membrane was distinct and angular (fig. 27, *b*).

Fig. 28 (case 3).—Capillary spaces in the tumor lined by neoplastic cells (H. and E.; × 1,200).

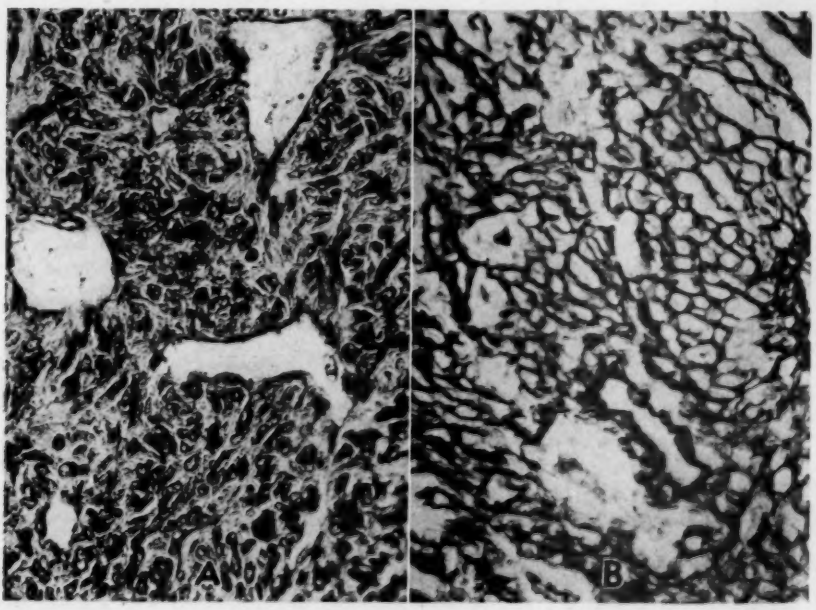


Fig. 29 (case 3).—*a*. Showing character of neoplastic cells and of their nuclei (H. and E.; × 300); *b*. showing network of reticulin laid down by the cells (Perdrau's method; × 300).

Another aspect of the tumor is represented in figures 27, *a* and 29, *a*. Here are shown numerous spaces which varied greatly in size and shape, and were frequently lined directly by tumor cells. The cells showed a tendency to group themselves around the spaces, their long axis often being perpendicular to the lumen. The structure in these areas suggested that of a so-called "perithelioma." The spaces, which usually contained no blood, were of different shapes—polygonal, diamond-shaped, cleft-like, etc., and often were not closed by endothelium, one part of their wall being made up of tumor cells themselves (fig. 28). The stroma in these areas also consisted of fine strands of reticulin which inclosed the cells individually (fig. 29, *b*).

The tumor cells infiltrated the adjacent brain tissue in a peculiar "Indian file" fashion (fig. 30), penetrating the healthy tissue in single or double rows of cells.

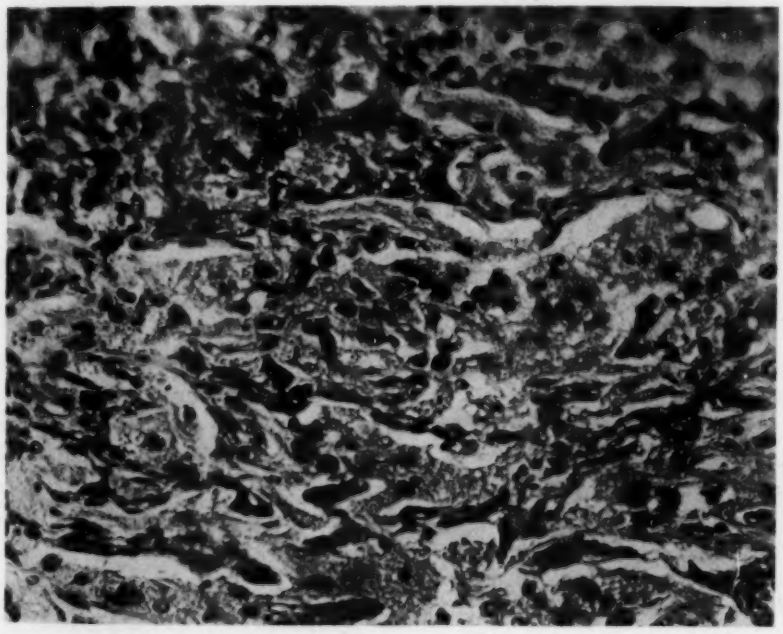


Fig. 30 (case 3).—Showing the advancing edge of the growth (H. and E.; ×300).

In some sections, cavities filled with serum were seen. Mitotic figures were readily found (fig. 27 *b*).

The structure of the tumor obtained at necropsy was identical with that removed a few months previously at operation.

Comment.—Throughout the patient's early sojourns in the hospital, we were laboring under the false impression that the lesion was a subtentorial meningioma. This, to be sure, is a rare situation for a meningioma to arise, and though these tumors have an abundant blood supply which often makes of an operation a formidable procedure, such unprecedented vascularity of the environmental tissues was beyond our

experience. In retrospect, therefore, it was poor judgment to have persisted in the attempts to re-expose the lesion. However, having no suspicion at the time that we were dealing with an angioma whose aneurysmal features were not as yet obvious, and being anxious at any cost to forestall blindness, we persisted in the successive and futile efforts to remove the supposedly innocent growth.

Whether from the outset there had been an extension of the tumor above the tentorium or whether indeed it may not have originated there is difficult to say. Had the negative ventricular tap been on the right side instead of on the left, it would be natural to assume that we had overlooked a right occipital lesion, and that the subtentorial portion of the growth that was first exposed was the least important part of it. The fact that the right occipital horn of the ventricle was successfully punctured in two of the early operations and that the fields of vision showed no objective or subjective constriction until nearly two years later, rather speaks against this view.

It, however, is possible that an early homonymous defect in the visual fields may have been overlooked through the long interval during which our attention was concentrated on the proved subtentorial lesion. It is quite possible, too, that the aneurysmal character of the lesion which had become outspokenly obvious by October, 1923, at the time of her fourth admission, was present two years before without being recognized and was what accounted for the excessive and uncontrollable bleeding that stood in the way of completing her early operations.

So far as we have seen, the literature contains no account of a solid hemangioblastoma of this sort that has become aneurysmal. That the lesion is a blood-vessel tumor there can be no doubt on histologic grounds, but it was an uncommon one not only in view of the bruit which developed but also in view of the invasive and locally malignant properties which it acquired. In this respect, it behaved more like some of the more rapidly growing and destructive types of meningioma than like any other angioblastoma we have seen.

Our experience goes to show that a meningioma is not affected favorably by radiation, though this tumor appears temporarily to have been. No meningioma in our series of some two hundred verified cases has ever become aneurysmal in character, though on auscultation a bruit has been heard in one or two of them.

From an operative standpoint we were doubtless, as events proved, attempting the impossible and that at great risk of life. Had we then had suitable electrosurgical methods at our disposal, the surgical problem, particularly at the last of the operations, would have been much simplified. The only consolation we may now have is that the patient was spared from blindness, and in spite of her long periods of hospitalization had a fairly comfortable two years which her happy disposition permitted her fully to enjoy.

The postmortem observations seem only in part to explain the clinical syndrome. The growth presumably started in the meninges over the occipital pole and spread by way of vascular connections into and through the lateral sinus to the subtentorial region, where it was first found. Why the cerebellar symptoms should have been primary and then have disappeared after the decompression is not so clear. Nor is it clear why the suboccipital decompression served permanently to relieve the choked disk. The difficulty experienced in tapping the ventricles is of course apparent. The terminal symptoms were in all probability due to the combination of the small abscess and the occlusion of the major sinuses by the growth.

COMMENT

If the foregoing photomicrographs and descriptions are compared with descriptions of hemangioblastomas of the peripheral tissues, it is at once evident that we are dealing here with what Mallory would call hemangio-endothelioblastomas growing largely without lumen formation.[9]

The origin of the reticulin in these tumors is not certain. In our own specimens, we were unable to demonstrate fibroglial or elastic fibrils. Collagen was rarely found, but reticulin was very abundant. The cells from which these strands of reticulin emanate contain a more elongated body and a more elongated nucleus, but seem in no other way to differ from the other cells of the neoplasm.

Mallory states that in such hemangio-endothelioblastomas "in time some of the fibroblasts around the vessels grow in and deposit collagen fibrils between the endothelial cells." This statement is evidently a deduction from his belief that endothelial cells never become fibroblasts, and that collagen and reticulin are essentially the same substance,[11] since it is obviously impossible for fibroblasts to grow into these tumors.

There is evidence from tissue cultures, however (Maximow[12]), that endothelial cells may transform themselves into fibroblasts, and we think it more reasonable to suppose that in these tumors the neoplastic endothelial cells may differentiate and form the strands of reticulin so characteristic of these growths. This opinion has recently been advanced also by Piney.[14]

The formation of true tumor giant cells, according to Lindau,[7] is also frequently seen in hemangioblastomas. They were a prominent feature of the tumor in our case 1. Myxomatous areas were found in all the tumors but were more extensive in the tumor in case 2. They have been interpreted by Livingston and Klemperer[8] in hemangiomas as undifferentiated mesenchymal tissue.

But the chief interest of these cases is in the fact that they lie on the borderline between the primary angioblastomas, which are true tumors of the brain and originate within its substance, and the primary

meningeal tumors that originate from the cerebral envelops. As was stated in the introductory paragraphs, the primary angioblastomas are, with few if any exceptions, tumors of the hindbrain. The meningiomas, on the other hand, are tumors that most often arise from the meninges over the cerebral hemispheres, and by far the greater number are found in the anterior portion of the cerebral chamber.

These meningeal tumors from their general appearance and manner of growth are almost unmistakable to the naked eye and represent one of the more common types of intracranial tumor. It is highly peculiar, therefore, that three of them which have originated from the meninges of the posterior part of the cerebral chamber should have been found to resemble in their microscopic structure the true hemangioblastomas of the cerebellum which have no apparent relation to the leptomeninges, though they have suffered from the unfortunate misnomer of being called "pial endotheliomas" in distinction to "dural endotheliomas."

That what appear to be true meningeal tumors should have been found to have a histologic structure so at variance with that which characterizes the usual meningiomas demands explanation. It is from a study of variants from the usual type of lesion that one sometimes gains a clearer idea of the histogenesis of the entire group.

The usual meningeal tumor known as a "dural endothelioma," with its typical cellular whorls, is too well known to need description. These tumors, as neurosurgeons appreciate perhaps better than others, are notable for their excessive extraneoplastic vascularity which makes their removal exceedingly difficult and hazardous when the growth is large and of long standing. A few of the tumors, what is more, on histologic examination show an excessive intraneoplastic vascularity, so that they are sometimes spoken of as *angioendotheliomas*. A vascular area from such a tumor is shown in figure 31, there being no indication, however, that the unusual vascularity is associated with the actual growth of angioblastic elements such as has been observed in the three cases of which we have given an account.

In our review of the literature, we have failed to find recognizable descriptions of any angioblastic meningiomas, with the possible exception of a case reported by Corten (1921)[2] as "hemangioma sarcomatodes." Similar tumors of course must have been encountered by other observers and must somewhere have been described, but very probably under designations that render them difficult to trace. The tumor in Corten's case was found post mortem in an infant who died of convulsions on the second day after birth. The growth, which was half the size of the fist, was found adherent to the tentorium, whence it projected into the temporo-occipital lobe without definite demarcation, whence the designation "sarcomatodes." Histologically, the tumor was an unmistakable mixed (cavernous, capillary and cellular) hemangio-

blastoma. The growth evidently originated from an extracerebral source, was incorporated with the dura over the posterior tentorium and projected into the brain. Aside from the fact that the tumor was found at such an early age, whereas the meningiomas are tumors of adult life (those of angioblastic type being no exception), the case has marked similarity to those we have described and doubtless is in some way related to them. Corten regarded his case as unique, and in describing it was obliged to fall back on the literature of the hepatic hemangiomas for comparative purposes.

The meningocyte from which these tumors appear to take their origin is a highly active cell which is normally present in the leptomen-

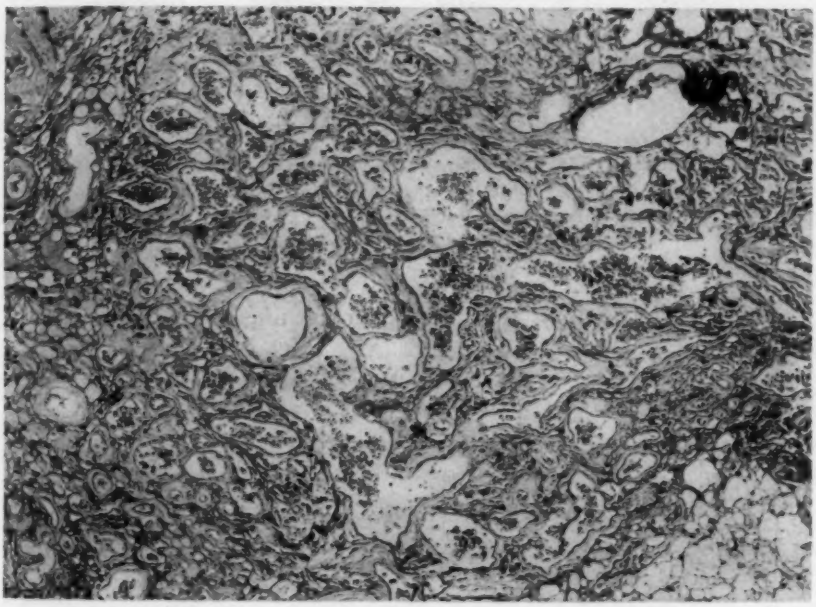


Fig. 31.—Highly vascular area in meningioma of usual type not due to newly formed blood spaces (H. and E.; × 80).

ingeal spaces, where, as one of us (Cushing)* has endeavored to show, it plays a most important physiologic rôle. These cells, which some prefer to call endothelial leukocytes, others clasmatocytes or histiocytes, represent the reticuloendothelial apparatus for the meningeal spaces. All of the meningiomas are found to be permeated with these cells, which, on a fresh smear, show an avidity for storing granules and a characteristic affinity for neutral red. They are easily cultivated in vitro, as we have found, and under these circumstances the growing cells appear to be capable of transformation into fibroblasts.

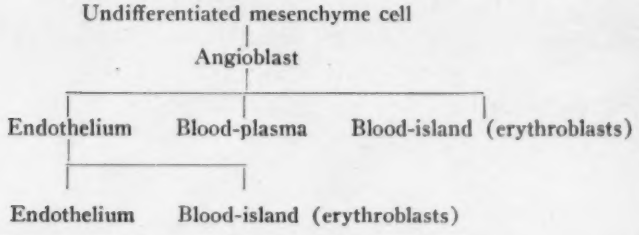
* The third circulation and its channels. Lancet, Lond., Oct. 24, 1925, ccix. 851-857.

Believing as we do that all of these isolated and bulky meningeal tumors have a common histogenesis, we are forced to the conclusion that the meningocytes from which they originate are capable of further subdivision, and that in all likelihood they are able to differentiate into angioblasts.

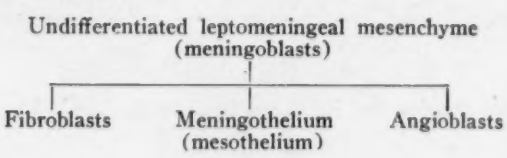
The origin of the vascular tissue of the body has long been a subject of controversy, but Sabin (1920)[16] seems definitely to have proved that the mesenchyme of the embryo is capable of forming new blood vessels *in situ*. The primitive mesoderm, by the splitting apart of two layers of cells, forms the celomic cavity, but as described by Sabin:

> The blood-vessels arise by the differentiation of a new type of cell from this same primitive mesoderm. This has a different cytoplasm from the original mesodermal cell, is more granular, more basophilic, and has new qualities, namely, the tendency to form solid masses which appear like a syncytium, the centers of which liquify to form blood-plasma, and a marked tendency to put out delicate sprouts by which it joins similar masses. These cells, or angioblasts, give rise to endothelium, blood-islands, and blood-plasma. All of the cells of the blood-islands of the first two days of incubation become erythroblasts. The lumina of the vessels are not formed of tissue-spaces, but rather by a process of cytolysis in the center of masses of cells or even within the cytoplasm of a single cell. An endothelial cell differentiates in its turn from the original angioblast. It can give rise to other endothelial cells or to erythroblasts.

This description may be expressed in the following diagram:



Reagan (1915)[15] showed that blood vessels may develop in the isolated head-fold of the chick, and Sabin has seen a portion of the ventral aorta of the head develop *in situ* in the living chick; but so far as we are aware, there are no observations on the earliest development of the vascular system of the leptomeninges. We do not know, therefore, whether the primitive mesenchyme of the leptomeninx is capable of differentiating angioblasts, but see no inherent difficulty in the hypothesis that such is actually the case. If this be true, we might make the following diagram explaining the variation in the cellular structure of the meningiomas.



There is one peculiarity of the three meningeal tumors which we have described as hemangioblastic in structure that deserves mention. Whereas the true hemangioblastomas of which we have previously given an account are relatively benign and slowly growing lesions that tend to produce cysts, the angioblastic meningiomas are solid lesions, and, to judge from these three examples, are rapidly growing, and, though they do not produce metastases, have a sarcomatous tendency.

This tendency, however, in the case of the meningiomas is not confined to those rare tumors having an angioblastic structure. The same sarcomatous tendency is shown by the meningiomas of other types. Certain of the tumors of the more common mesothelial type, even after they have undergone extensive psammomatous change, may take on a period of active growth; and it is well known to surgeons that some of the softer tumors are most prone to recur after an apparently total removal and to grow with great rapidity. The same thing appears to be true of the more essentially fibromatous tumors, and occasionally one meets with a recurrent tumor primarily of the common mesothelial type which has acquired the histologic appearance of a dense fibrosarcoma.

Accordingly, therefore, though the term meningioma serves to connote a meningeal tumor of definite and unmistakable sort, the cellular components of the growth (meningoblasts) are apparently capable of differentiating into meningothelial (i.e., endothelial or mesothelial), fibroblastic or angioblastic types, and possibly indeed into osteoblasts [1 and 5] and other types of cells. What is more, any one of these cellular types may develop sarcomatous tendencies.

CONCLUSIONS

The problem of the endotheliomas has led to much controversy. Because the term "endothelioma" usually brings to mind the endothelium of blood vessels, the designation of the common tumor of the meninges as "dural endothelioma" is unfortunate.

The term meningioma represents in our estimation a noncommittal and convenient common denominator for all of these lesions. The fact that some few of these tumors possess the architectural features of a hemangioblastoma indicates that the meningoblasts are capable of differentiation into angioblasts. They may also form fibroblasts and possibly other types of cells.

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PECULIAR STRUCTURES IN THE MYOCARDIUM OF THE DOMESTIC FOWL*

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The bodies to be described were discovered accidentally in the routine study of the myocardium of a white leghorn pullet. The bird was obtained from a farm in Windham County, Conn. The flock is an unusually healthy one.

EXPERIMENTAL WORK

On Oct. 21, 1927, the chicken had received into the right pectoral muscle an injection of 1 cc. of a suspension of brain and spinal cord from a paralyzed fowl, containing arsenous acid in a dilution of 1 : 150,000. In the left pectoral muscle it had received an injection of 1 cc. of arsenous acid in a dilution of 1 : 150,000. Symptoms did not develop following the inoculation, either locally or generally. On Dec. 9, 1927, the chicken received 5 cc. of a 5 per cent solution of saccharated ferric oxide intravenously; on the following day, it was killed by ether and exsanguination.

Autopsy.—There was marked anemia, with an excess of subcutaneous and intra-abdominal fat. Gross lesions were not found in the pectoral muscles at the site of the inoculation. The viscera did not show any noteworthy change. The small intestine contained numerous cestodes (species not identified), several *Heterakides perspicillae* and the usual representation of *Heterakis papillosa* in the cecum. Microscopic study of the tissues did not disclose lesions of particular interest. There was an abundance of stainable iron in the Kupffer cells and in the reticulo-endothelial cells of the spleen. A few coccidial cysts were present in the duodenal mucosa.

The sections of the myocardium, fixed in Zenker's solution, presented a surprising picture. Within the fibers were many foreign bodies. The smallest measured not more than 2 microns in their longest diameter; the largest 18 by 11 microns. They were variable, some being oval, some triangular or wedge-shaped, with rounded corners, and some spherical or navicular. The bodies appeared to have a certain plasticity; where they were crowded together, the individuals were more or less faceted, or, in other words, their contiguous surfaces were flattened. Occasional forms were seen with bulbous pseudopodial projections.

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Staining Reactions.—The bodies were easily stained in a variety of ways, as follows:

Stain	Color of Bodies	Color of Nuclei of Muscle Cells
Hematoxylin-eosin	Pale grayish blue	Dark blue
Heidenhain's iron hematoxylin	Dark gray or black	Dark gray with vesicular structures
Giemsa's	Deep purple	Pale blue
Eosin-methylene blue	Blue	Pale blue
Gram's gentian violet, counterstained with safranin	Purplish	Red
Methyl green-pyronin	Bright red	Pale greenish blue
Mallory's anilin blue-orange G.	Brilliant orange red	Red
Mallory's iron stain	Negative	
Von Kossa's silver, for calcium	Negative	
Carbolfuchsin, followed by 5 per cent nitric acid	Not acid-fast	
Iodine	Unstained	
Nitric acid, 10 per cent	Not dissolved	

In unstained fixed preparations, the bodies were distinctly more refractile than the muscle nuclei.

Structure.—Little internal structure could be distinguished. Many forms showed fairly definitely a well stained envelop or cortex with one or sometimes many central vacuoles or circular areas, which stained more faintly. Within these, there was at times a central granule or small rodlike structure. In some of the bodies, the appearance suggested a nucleus and karyosome; but there was never a definite nuclear membrane, and it was impossible to be certain that these structures represented nuclei.

Location.—The bodies lay within the sarcoplasm often aggregated in the vicinity of a nucleus. Sometimes they were arranged in rows with long axes parallel, and more or less at right angles to the axis of the fiber. More often there was not a definite arrangement.

Effect on the Muscle-Fiber.—Where the bodies were numerous, the fibers were distinctly swollen. With Mallory's phosphotungstic acid hematoxylin stain, the myofibrils were seen to be spread apart, and occasionally ruptured, an appearance suggesting a certain amount of ameboid motility on the part of the bodies. The sarcoplasm was coarsely granular in the vicinity, but did not show evidence of coagulative necrosis. The nuclei of the muscle fibers were well stained and did not give any evidence of degeneration. Rarely they appeared somewhat swollen and hydropic.

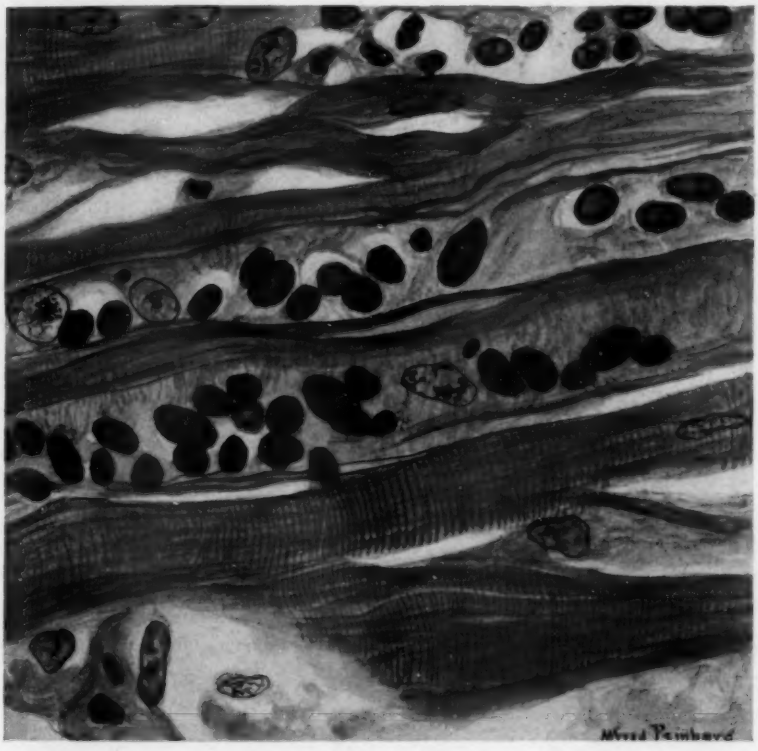
Sometimes, the bodies lay within distinct cystlike spaces, or in multilocular cavities separated by bridges of sarcoplasm.

A cellular reaction was not seen in the adjacent connective tissue, nor was any increase in the connective tissue fibers to be observed. The bodies did not provoke any inflammatory reaction.

Since the discovery of this first case, identical bodies have been found in the myocardium of four other chickens—not, however, in large numbers.

In the available literature, reference has not been found to the occurrence of similar bodies in the myocardium of the fowl, and it has been impossible to arrive at any decision as to their nature. Various possibilities have suggested themselves:

1. They are products of degeneration, possibly of the nature of crystalloids. Against this view may be urged the absence of degenerative changes in the nuclei of the muscle fibers; the cytoplasm likewise shows only such alteration as can readily be accounted for by the mechanical



A section of the myocardium of a chicken. Certain unidentified, remarkable bodies are revealed within the sarcoplasm. Giemsa's stain was used, and Leitz ocular 3, objective 7.

displacement of the myofibrils. Crystalloids, such as the Reinke bodies within the Leydig cells of the testis, stain with eosin and not with basic stains.

2. The bodies are yeasts, blastomycetes, or torulas. Against this is the absence of a doubly refractile membrane, of budding forms, and the great polymorphism of the structures. Moreover, it seems likely that an infection with pathogenic yeasts would be accompanied by an inflammatory reaction.

3. The bodies are protozoan parasites of undetermined nature. Sarcosporidia occurs in the skeletal muscles of fowl (Kuhne,[1] Rivolta[2] and von Ratz[3]), but their presence in the myocardial fibers has not been recorded. The bodies in question do not at all resemble sarcosporidial cysts with their contained falcate sporozoites, and cannot be identified with any of the known species. It is possible that the fixation (Zenker's fluid without acetic acid) was inadequate to conserve the internal structures of the bodies, because of failure to penetrate the capsular substance. Whatever the reason, the structures are too little differentiated to permit their definite identification as protozoa.

4. They are cytoplasmic inclusions, possibly associated with the presence of a virus. In their form and staining reactions, these structures present little resemblance to any known inclusions associated with a "virus." The suggestion is purely speculative.

Although it is impossible to verify or disprove any of the foregoing hypotheses, it seems worth while to call attention to the remarkable bodies, in the hope that others may have opportunity to study them in fresh tissues, and to investigate them further.

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THE FORMATION OF ABSCESSES IN AN INFECTION WITH BACTERIUM MONOCYTOGENES*

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In the course of a series of experiments in which rabbits were infected with *Bacterium monocytogenes* to produce a monocytosis, small abscesses developed in many of the viscera of some of the animals. The results of these experiments, so far as they pertained to the origin of the monocyte of the blood, were published.[1] It was pointed out in this paper that the cellular response of the rabbit to this bacterium could be divided into two types. One of these, which I termed the generalized reaction, consisted of the production of the monocytosis. The other, or local reaction, resulted in the formation of abscesses at those points where colonies of bacilli had settled in the tissues. The former was elicited by relatively small doses of the bacterium. The local reaction usually ensued in those animals that had been infected with large doses of the bacterium or with doses particularly virulent. It could be seen in the later stages of the infection and apparently was unrelated to the production of the circulating monocytes. Because of the great length of the paper just referred to, it was necessary to make but scanty mention of the local reaction.

It was shown in this first paper that the fixed cells of the body did not partake directly in the formation of the circulating monocytes. It was also shown that the monocytes developed intravascularly—for the most part, in the sinuses of the liver and the spleen—by the individual transformation of circulating lymphocytes, and that the so-called monoblasts of certain hematologists, are, by all present hematologic and histologic criteria, identical with lymphocytes. Careful attention was paid throughout this work to the reactions of certain of the fixed cells of the body—the adventitial cells of Marchand and the embryonic mesenchymal cells of Maximow and Volterra—in order to find evidences of their turning into monocytes; for these fixed cells had been repeatedly shown to have great abilities for differentiation into lymphocytes and myelocytes, as well as into phagocytes, in inflamed tissues. In those rabbits in which only the generalized reaction was present, few mitotic figures were found in these fixed cells. The evi-

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* This work was conducted under a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

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dences of division of cells should have been present in great numbers if the newly formed monocytes developed directly from the fixed cells. Besides, not any where was there evidence of these fixed cells rounding off and becoming transformed into monocytes.

In those rabbits which developed abscesses as a result of the infection, there were some interesting pictures of the origin and development of the mononuclear exudative cells in the affected areas of the tissues. It is the purpose of this paper to describe some of the characteristics of the abscesses due to *B. monocytogenes* injected intravenously. In order to complete the study, I also injected this bacterium subcutaneously to observe the reaction of this tissue to the organism.

This work was conducted under the direction of Dr. A. A. Maximow in the Department of Anatomy of the University of Chicago.

MATERIAL AND METHOD

Into adult rabbits was injected intravenously one half the growth of a twenty-four hour agar slant of *B. monocytogenes* strain 53. The peripheral blood of an ear vein was studied every few hours for the appearance of the monocytosis, by supravital, dry and wet smears. The animals were killed at various intervals of time after the development of the monocytosis. At autopsy, parts of the various tissues were studied in supravital, dry and wet smears, and the remainder of each organ was fixed in Zenker-formaldehyde solution, embedded in celloidin, cut in serial sections and stained with hematoxylin-eosin-azure II. The details of the experiments are to be found in my previously mentioned paper. In the case of the experiments with the subcutaneous injections, the subcutaneous tissue, together with the subjacent muscles, was fixed at various intervals of time on a cork frame in Zenker-formaldehyde solution. They were embedded in celloidin and cut in serial sections parallel to the flat surface of the tissue. They were then stained in hematoxylin-eosin-azure II. The bacteria in all of the tissue stained well with azure.

OBSERVATIONS

In several of the viscera of certain of the rabbits, particularly of those into which virulent strains of the bacteria had been injected, small areas of necrosis were seen at autopsy. They were found in the spleen, liver, suprarenal glands and lungs. In most of the organs, they were about 1 mm. in diameter, and light grayish yellow; in some cases, they were as large as 3 mm. Under the microscope, the abscesses varied from areas involving but a small collection of cells to some much larger than a low power field.

Liver and Suprarenal Gland.—In these organs, the smallest foci consisted of a few necrotic parenchymal cells, which were infiltrated by a few special leukocytes and mononuclears. In the capillaries about these small foci were large numbers of closely packed leukocytes and agranulocytes. The littoral cells in or near the affected areas were somewhat swollen and their nuclei were large and vesicular. Such cells were

different from the resting littoral cells in the surrounding uninjured tissue. Occasionally, a large littoral cell might be seen rounding off and evidently becoming a free macrophage. Such figures were rare. Mitotic figures in these local fixed cells were not observed. Accordingly, an important part in the production of the small mononuclear cells could not be ascribed to them. In these early stages in the formation of the abscesses, the capillaries were filled with leukocytes and agranulocytes, and these cells were also seen migrating from the vessels into the necrotic parenchymal cells. Large numbers of bacilli—singly or in pairs —were seen in most of these areas of necrosis.

In slightly larger, older abscesses, the necrotic cells were much more numerous, and the involved area was much larger. In such places, the center of the focus usually contained, besides the debris of dead cells, some fibrin and many bacilli. Many ameboid special granulocytes and exudative mononuclear phagocytes (polyblasts) were scattered through the dead cells. The polyblasts were connected by a complete series of transitional forms with the blood lymphocytes and monocytes at the margin of the abscess. The littoral cells showed but few signs of activity even in the largest abscesses.

In the earliest stages of the abscesses, the mononuclear cells were still typical lymphocytes and monocytes. As the abscess became larger, many of the lymphocytes and monocytes began to disappear from the center of the abscess and their place was taken by the polyblasts. The multitude of transitional forms between the agranulocytes and the polyblasts clearly indicated the origin of the latter from the former.

At the margin of the medium-sized and large abscesses was a thick wall of lymphocytes and monocytes. These cells also plugged the surrounding capillaries for surprising distances. These agranulocytes were rarely rounded; they usually showed evidences of ameboid activity and many of them were seen to migrate into the abscessed area. The special granular leukocytes were much less numerous in the later stages of the formation of the abscess. Mitotic figures were exceedingly rare in all of the abscesses in these animals. After a careful study of this material, it became apparent that the swarms of special granular leukocytes and practically all of the exudative mononuclears were of hematogenous origin.

The sharp separation of the hematogenous and histogenous exudative cells was clearly demonstrated in those abscessed rabbits into which lithium carmine had previously been injected. In such rabbits, the mature or phagocytosing littoral cells of the sinuses of the liver (Kupffer cells) and of the cortex of the suprarenal gland were clearly seen because of their carmine inclusions. Such carminized cells did not take part in the production of the mononuclear exudative cells, for the latter practically never contained any of this material.

Free bacilli could frequently be found in great numbers in and about the abscesses. In the liver in some of the animals there was also a great periportal infiltration with various-sized lymphocytes and monocytes. The striking point about these abscesses in the liver and the suprarenal gland was the fact that the transitional forms between lymphocytes and monocytes, on the one hand, and the polyblasts, on the other, were so numerous that it was impossible to draw a line of distinction between the three groups of cells.

Spleen and Lymph Node.—More striking than in the liver and suprarenal gland, however, was the appearance of the abscesses in the spleen and the abscess which was found in only one of all the lymph nodes of the rabbits used in this work. At the periphery of the abscesses of the spleen, the direct transformation of lymphocytes into monocytes could be followed with great ease. The nucleus of the former became slightly elongated, a little larger and definitely more vesicular. The protoplasm increased somewhat in amount, and a lightly staining centrosphere became visible at the indentation of the nucleus. The histiocytes—the littoral cells, as well as those of the pulp cords—did not develop into monocytes. This was well shown in carminized animals, for none of the cells within the abscesses contained carmine. The cells of the embryonic reticulum could at times be seen to retract their processes and to become basophilic, and to develop rather prominent nucleoli, but these were different in appearance from the typical monocytes and smaller polyblasts.

The clearest demonstration of the participation of these various cells in the formation of the abscesses was shown in the small abscess which was found in one of the lymph nodes. The abscess in this case involved a follicle with its germinal center. The center of the abscess consisted of the debris of dead cells, a few rather scattered, large, exudative polyblasts, some heavy strands of fibrin and a few special leukocytes. Toward the margin of the abscess, the large polyblasts became scarcer and the smaller cells more frequent. Scattered throughout the area were a few diplobacilli. In the marginal zone, there was a mass of relatively small mononuclear cells which were difficult to identify. Many of them were typical monocytes. They had relatively pale nuclei, minute nucleoli, and comparatively large amounts of cytoplasm. They were usually highly ameboid. These cells were connected with the typical lymphocytes of the lymphoid tissue at the periphery of the abscess by countless transitional forms. Lymphocytes undergoing this transformation are represented in figures 1 and 2. Figure 1, portraying a field somewhat nearer to the center of the abscess, shows the exudative mononuclears just mentioned; many of them are seen to have nuclei typical of the lymphocyte, but with slightly increased amounts of

cytoplasm. In figure 2, practically the entire field is covered with cells that represent transitions between lymphocytes and monocytic polyblasts. In fact, nearly all of the cells seen in figure 2 are of this character. Scattered between the smaller mononuclear cells in the periphery of the

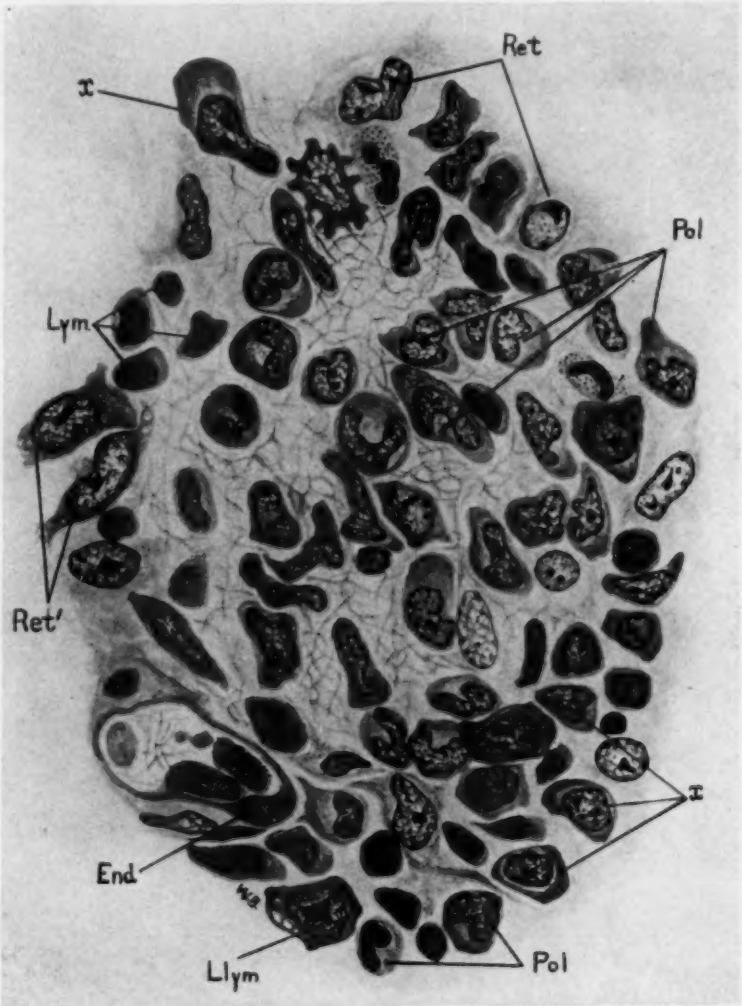

Fig. 1.—A drawing of the microscopic aspect of a section from the wall of an abscess in a lymph node of a rabbit injected with a virulent strain of *Bacterium monocytogenes*. *X* indicates transitional forms between lymphocytes (Lym) and polyblasts (Pol) in the center of the figure. *Ret* designates embryonic reticulum cells. *Ret'* points to stages in the transformation of the latter into large polyblasts. The inactivity of the endothelial cell (End) of the capillary may be seen. (Camera lucida at level of microscope stage. Leitz 2 mm. apochromat objective and 10 × periplan ocular.)

abscess one can follow the rounding up and the increase of basophilia of the embryonic reticulum cells. Such cells are indicated by *Ret'* in figures 1 and 2.

This abscess offers a crucial point for the determination of the rôle of the lymphocytes and the cells of the reticulum in the production of

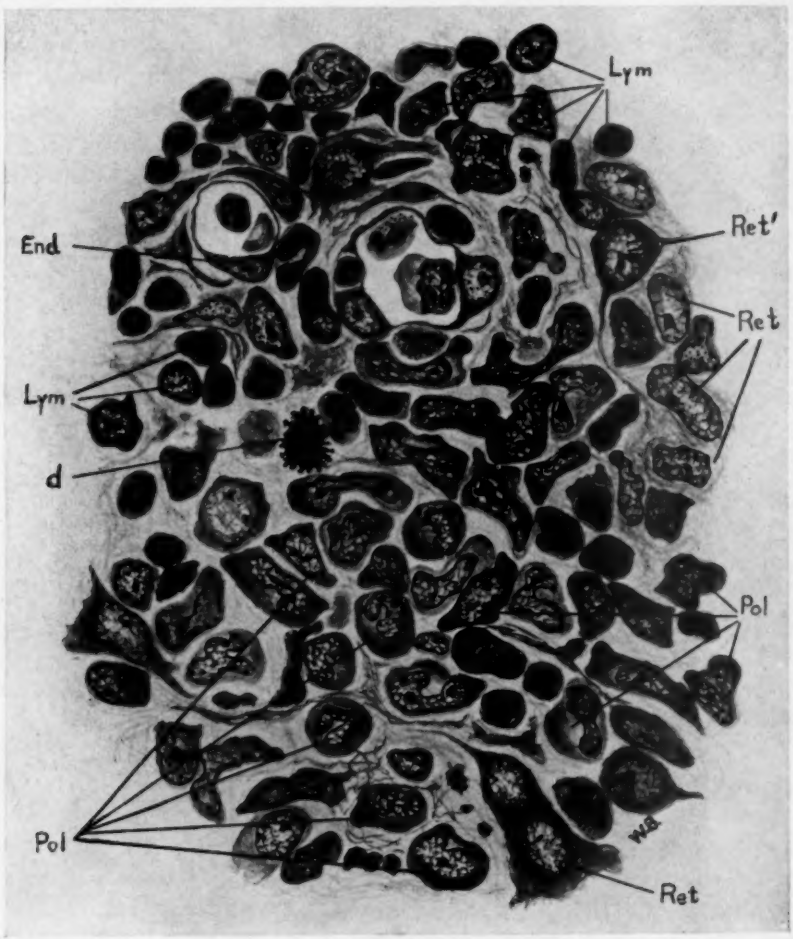

Fig. 2.—A drawing of the same abscess as represented in fig. 1, but of a field closer to the unaffected surrounding lymphoid tissue. (Abbreviations and optical system as for fig. 1.)

monocytes. The embryonic reticulum cells in this abscess did not play a part in the production of the smaller active defense cells. Their transformation into the large exudative cells could, however, be followed clearly, although the process was limited because of the relatively few cells of the reticulum present in the affected area, and mitotic

figures did not occur. In the abscesses of the suprarenal gland and the liver, the mononuclear exudative cells could be traced with great ease to lymphocytes and monocytes within the capillaries surrounding the abscessed area. In the abscess in the lymphoid tissue, as was so clearly shown in that occurring in the lymph node, the direct transformation of the lymphocytes preexisting in this tissue was clearly seen. The monocytic change in the lymphocytes of the follicle as well as in those at some distance from the abscess was marked and was exhibited by all types of lymphocytes. In my paper on the origin of the monocytes, it was shown that the lymphocytes of the lymph nodes did not turn into monocytes in most of the rabbits. In three rabbits of the series (one was heavily carminized and the other two had been splenectomized and then had had Higgins' India ink injected into their portal veins before the injection of *B. monocytogenes* intravenously), many of the lymphocytes in the lymph nodes became monocytoid and some of them developed into typical monocytes.

Subcutaneous Tissue.—When a suspension of *B. monocytogenes* was injected into a rabbit under the skin, the resultant inflammatory reaction developed in much the same way as reactions due to other inflammatory stimuli. In sections of such material, in from ten to fifteen hours and even later after the injection, one found convincing indications of the hematogenous origin of the mononuclear exudative cells. If the sections were not too thin—that is, from 10 to 12 microns thick—with careful focusing one found great numbers of migrating special leukocytes, lymphocytes and monocytes. If the walls of the capillary veins and capillaries were examined carefully, one saw that many apparently rounded cells within the vessel lumen had processes, capped with small knobs, extending into or through the endothelial cells (fig. 3, Lym'). Monocytes, lymphocytes and granular leukocytes were also to be found within the vessel walls, particularly of the capillary veins. Sometimes five and six migrating lymphocytes could be seen in various stages of their passage through the wall of a small vessel. The endothelial cells were slightly swollen and basophilic but did not show evidence of rounding off and becoming free (fig. 3, End.). The various perivascular cells were usually inactive, although an occasional perivascular phagocyte could be seen to mobilize.

Just outside the vessels were large numbers of ameboid mononuclear cells which varied in size from the smallest lymphocytes to ameboid monocytes and polyblasts (fig. 3, Pol.). Closer to the center of the abscessed area one could trace all the stages in the transformation of the hematogenous mononuclear cells into the larger characteristic mononuclear exudative cells, or polyblasts (fig. 4, Pol.). These cells were everywhere interspersed with granular leukocytes (fig. 4, Spec.), and

forming a background to the picture were the swollen fibroblasts (fig. 4, Fib.). Evidence of the fibroblasts contracting into polyblasts was not found. The fibroblasts, except for an occasional mitosis, remained inactive throughout the inflammatory process. In edematous areas they might round off, but on the whole, they retained their extended shapes. Sometimes they became swollen. In the early stages of the process—

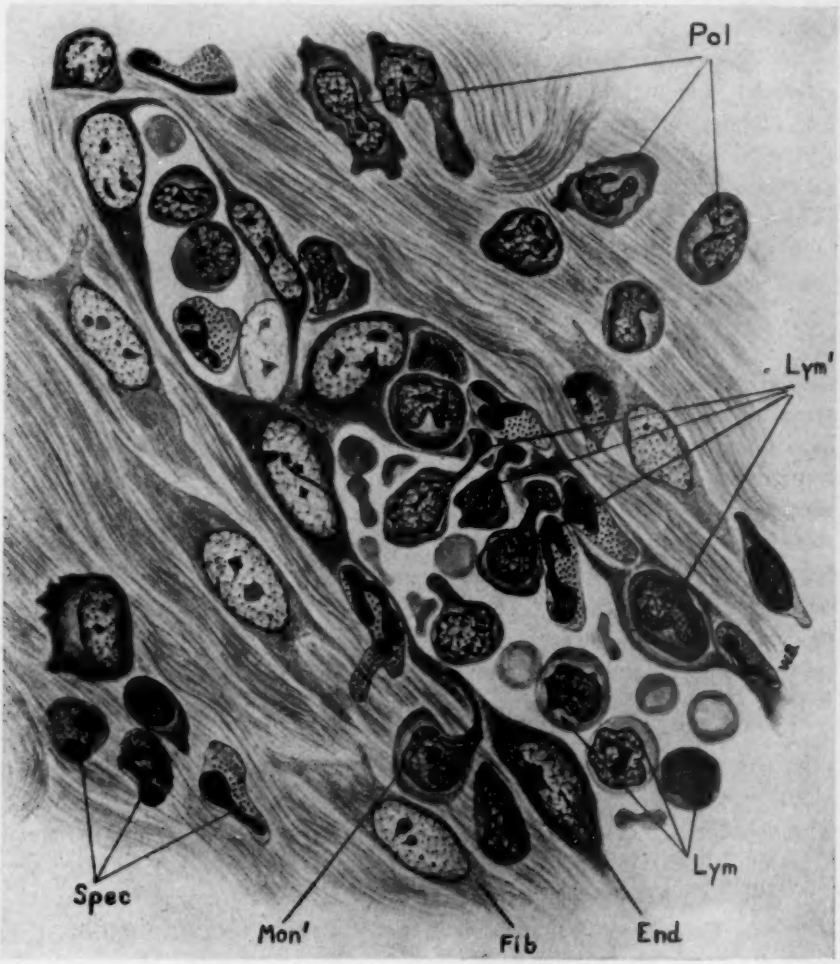

Fig. 3.—A drawing of the microscopic aspect of a section from the periphery of the abscess following subcutaneous injection of *B. monocytogenes* thirty-six hours previously. *Fib* indicates a fibroblast; *End*, swollen basophilic endothelial cells. *Lym*, lymphocytes; *Lym'*, migrating lymphocytes; *Spec*, special granular leukocytes; *Pol*, polyblasts (hematogenous); *Mon*, a migrating monocyte. (Camera lucida at level of microscope stage. Leitz 2 mm. apochromat objective and 12 × periplan ocular.)

when the area was first flooded with the small polyblasts and agranulocytes—the fibroblasts were distinctly a cell apart. In later stages, when some of the smaller polyblasts had begun to enlarge, the fibroblasts were much less prominent. On careful search, they could still be found as inactive cells obscured by the great number of exudative mono-

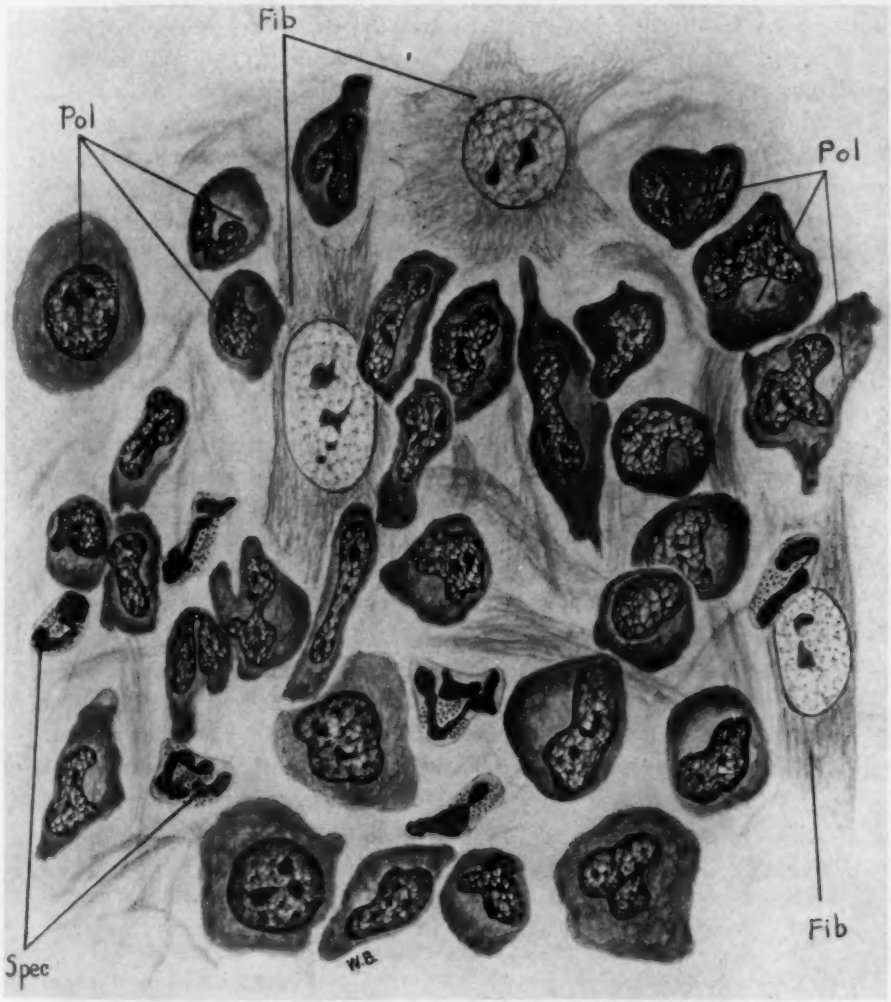

Fig. 4.—A drawing of the same abscess as represented in fig. 3, but of a field closer to the center of the affected area. It shows the inactive fibroblasts *(Fib)* and the hypertrophying polyblasts *(Pol)*. (Same optical system for fig 3.

nuclears. The hematogenous origin of the granular leukocytes was also clear. With the agranulocytes, the special leukocytes migrated from the vessels in great numbers. Outside the vessels, they were highly ameboid

and congregated in great array about the bacteria in the center of the injected area. In the earlier stages of the inflammation, the granular leukocytes were much alive. At the end of twenty-four hours, however, many of them had begun to disintegrate, and their granules became free.

This explains one of the obvious mistakes into which von Möllendorf [2] and Stockinger [3] recently have fallen. These authors interpreted the presence of these phagocytosed granules—they did not mention the phagocytosed nuclear debris which is also often present—in the exudative mononuclears as proof of the origin of all of the granular leukocytes in the inflamed area from the local preexisting fibroblasts and histiocytes. They failed to realize that such pictures were found only after the special leukocytes had begun to die; they were not found in the earlier stages of the inflammation, when the sudden, rapid appearance of myriads of special leukocytes in the affected area was only to be explained as due to a hematogenous source (see following).

The subcutaneous abscesses due to *B. monocytogenes* differed from those due to the ordinary pyogenic bacteria and from the reaction to trypan blue only in that among the migrating agranulocytes a somewhat higher percentage of monocytoid lymphocytes was present. In other words, the chemotactic stimulus in the case of this infection was of such a character that it accentuated or even hastened the polyblastic change of the blood lymphocytes. It was during the earliest stages in the polyblastic change in the lymphocytes that many of the latter passed through a monocyte or monocytoid stage (Bloom [4]). It is for this reason that Maximow,[5] in several recent publications, considered the monocyte to be the "physiological polyblast" of the blood.

From the foregoing, it is seen that the reaction of the subcutaneous tissue to the presence of this bacterium was analogous to that which occurred in the previously described abscesses in the various viscera. The fibroblasts were unaffected by the presence of the bacteria; the few local, preexisting histiocytes contracted into large, rounded polyblasts of the character of macrophages; the great burden of the defense reaction was born by the hematogenous monocytes, lymphocytes and special leukocytes. Because of the countless number of hematogenous elements one had an excellent opportunity to follow all of the stages in the trans-

2. Von Möllendorf, W., and M.: Das Fibrocytennetz im lockeren Bindegewebe, seine Wandlungsfähigkeiten und Anteilnahme am Stoffwechsel, Ztschr f. Zellforsch. u. mikr. Anat. **3**:503, 1926; Die örtliche Zellbildung in Gefässwanden und im Bindegewebe, München. med. Wchnschr. **73**:135, 1927.

3. Stockinger, W.: Zellbilder und Zellformen des menschlichen Bindegewebes, Ztschr. f. d. ges. exper. Med. **58**:777, 1928.

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formation of the mononuclears of the blood into exudative polyblasts. In the abscesses in the lymphoid tissue, the direct transformation of the local, preexisting lymphocytes into monocytes and macrophages was clearly shown. In both the subcutaneous tissue and the lymphoid tissues, a very small part of the large macrophages could be traced to local cells—to the tissue histiocytes in one case and to the embryonic reticular syncytium in the other.

COMMENT

In the processes of inflammation—aseptic or purulent—the exudative polyblasts come, for the greater part, from the emigrated agranulocytes of the blood. A few of them also arise from the local resting wandering cells, (histiocytes, clasmatocytes). These round off and become active ameboid phagocytes. The outstanding features in inflamed tissues in the early stages of the process are the swarms of small exudative mononuclears and agranulocytes together with the special granular leukocytes. The number of large phagocytes at this stage is small. Mitotic figures are infrequent among these cells and are insufficient to provide for the countless numbers of small phagocytes which fill the inflamed area. In carminized animals, in the early stages of inflammation, the agranulocytes and most of the small polyblasts do not contain any carmine. This certainly indicates that these cells have not come from the local histiocytes, for these are filled with the carmine particles. As the polyblastic change becomes more marked, the smaller cells begin to store carmine granules.

The foregoing is the description of the inflammatory process which was made by Maximow [6] and sustained by him in an extensive series of researches during the past quarter of a century. It is this process which is described and pictured in the present paper on the inflammatory reaction due to infection with *B. monocytogenes*. It differs from the earlier views of Marchand [7] only in deriving the majority of the exudative cells from the agranulocytes of the blood rather than from the local phagocytes (including Marchand's adventitial cells). My observations are, however, in marked disagreement with the view held by Marchand [8] since the publication of the work of G. Herzog.[9] Accord-

6. Maximow, A.: Experimentelle Untersuchungen über entzündliche Neubildung von Bindegewebe, Beitr. z. path. Anat. u. z. Pathol. (supp.) **5**:1, 1902; Beiträge zur Histologie der eiterigen Entzündung, ibid. **38**:301, 1905.

7. Marchand, F.: Referat über die Herkunft der Lymphozyten und ihre Schicksale bei der Entzündung, Verhandl. d. deutsch. path. Gesellsch. **16**:5, 1913.

8. Marchand, F.: Die örtlichen reaktiven Vorgänge (Lehre von der Entzündung), in Krehl and Marchand: Handbuch der allgemeinen Pathologie, Leipzig, S. Hirzel, 1924, vol. 4,[1] p. 70.

9. Herzog, G.: Experimentelle Untersuchungen über Einheilung von Fremdkörpern, Beitr. z. path. Anat. u. z. allg. Pathol. **61**:377, 1916.

ing to this writer, the inflammatory exudative cells arise practically exclusively from the somewhat vague "Gefässwandzellen." In neither Marchands' latest monograph [8] nor in any of Herzog's papers is there a clear description in either words or pictures of the endothelial (common peripheral vascular endothelium) origin of the exudative cells.

During the past few years von Möllendorf has claimed that the fibroblast is the exclusive source or stem cell for all of the phagocytes, including the granular leukocytes in inflamed tissues. In spite of the avidity with which this theory has been accepted as fact by many German investigators, evidence is not found in any inflamed tissues for this reputed cytopoietic activity on the part of the fibroblasts. Von Möllendorf's experiments were criticized by Aschoff [10] and Lubarsch [11] and they were repeated with his technic by Maximow,[12] Büngeler [10] and most recently by Gerlach and Jores.[13] None of these writers found the slightest evidence in favor of the correctness of von Möllendorf's views. For they found that the fibroblasts played a passive rôle in the early stages of the inflammation. After some days the fibroblasts did, however, become active in producing a part of the scar tissue.

I had the opportunity of examining some of von Möllendorf's own preparations. I was unable to find any traces of the transformation of the fibroblasts into phagocytes (polyblasts) and leukocytes, which he asserted was apparent in these very slides.

The material described in the present paper clearly demonstrated the marked migration of the agranulocytes from the blood vessels into the injured area and their hypertrophy there into small and larger macrophages. This polyblastic change of the emigrated lymphocytes took place in exactly the same manner as the change which I described for the lymphocytes in tissue cultures of the lymph of the thoracic duct of the rabbit.[4] There was not any indication in my sections of the vascular endothelium becoming transformed into phagocytes. When an aseptic foreign body was introduced into lymphoid tissue (Babkina [14]), most of the exudative cells in the early stages were large and were derived from the cells of the reticulum. It was only in the later stages that the local lymphocytes hypertrophied into polyblasts. In the abscess of the

10. Aschoff, cited in Büngeler, W.: Uber Leukozytenbildung aus Histiozyten, Verhandl. d. deutsch. path. Gesellsch. **22**:243, 1927.

11. Lubarsch, cited in Büngeler (footnote 10).

12. Maximow, A.: Morphology of the Mesenchymal Reactions, Arch. Path. **4**:557 (Oct.) 1927.

13. Gerlach, W., and Jores, A.: Die Herkunft der Exsudatleukozyten bei der akuten Entzündung, Virchows Arch. f. path. Anat. **267**:551, 1928.

14. Babkina, H.: Changes of the Tissue of Blood Forming Organs in Aseptic Inflammation, Inaugural Dissertation, St. Petersburg (Russian); abstr., Folia haemat. **11**:202, 1910.

lymph node previously described, which was provoked by the colonization of bacilli, the clear-cut direct transformation of the local lymphocytes into monocytoid cells and polyblasts was obvious (figs. 1 and 2).

SUMMARY

1. Abscesses in the liver and the suprarenal gland of the rabbit caused by intravenous injection of *Bacterium monocytogenes* were delimited by the circulating lymphocytes and monocytes. These were the cells which were transformed into the exudative mononuclears of the abscesses. The local histiocytes played an insignificant part in the abscesses.

2. In the abscesses of the spleen and the lymph node, the local lymphocytes became polyblasts. Some few of the cells of the reticular syncytium also turned into large phagocytes. Mitoses were infrequent in these cells.

3. The phagocytes of the abscess resulting from the subcutaneous injection of *B. monocytogenes* were practically exclusively of hematogenous origin.

4. In none of these inflamed tissues was there any evidence in favor of the special leukocytes and exudative mononuclear phagocytes (polyblasts) developing from either fibroblasts (von Möllendorf) or from vascular endothelium (Mallory, Herzog).

THE DEFENSIVE AND METABOLIC APPARATUS OF THE LUNGS

THE LUNGS AND THE MACROPHAGE SYSTEM *

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The French physiologist Fort,[1] in a study published in 1867, expressed the belief that the lungs display characteristics proper to secretory organs. From an anatomic standpoint, he found structural similarities between these organs and glands, and accordingly he spoke of the pulmonary gland—la glande pulmonaire. In recent publications, Roger [2] used interchangeably the terms lung and gland, and Aschoff [3] found that "strictly speaking the acinus of the lungs corresponds to the lobes of a glandular organ."

Apparently the functions of the lungs are as complex as is their structure. Physiologic investigations suggest that the lungs play a rôle in the metabolism of lipoids. Roger [2] compared the pulmonary action on fatty substances with the action of the liver on carbohydrates. This comparison was suggested by the fact that absorbed albumins and carbohydrates pass directly into the liver, while fatty substances are transported by way of the lymphatics and the thoracic duct to the right side of the heart and the lungs. Roger, Rathery, and Binet,[4] in experiments on dogs, found that the lungs act also on the blood sugar. Two opposite processes occur in the "pulmonary gland," according to these authors: a formation of free sugar and a simultaneous more or less complete destruction of the liberated sugar. Mauriac and Dumas [5] stated that the glycolitic action of the lung tissue in vitro is superior to that of the majority of other tissues. It has also been claimed (Roger) that alkaloids and various other toxic substances are oxidized in the pulmonary parenchyma. Kosaka,[6] in perfusion experiments, found that phenol placed

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1. Fort: Anatomie et physiologie du poumon considéré comme organ de secretion, Paris, A. Delahay, éditeur, 1867.

2. Roger, G. H., and Binet, Léon: Recherches sur la physiologie du poumon, Rev. de méd. **42**:1, 1925.

3. Aschoff, L.: Bemerkungen zur Physiologie des Lungengewebes, Ztschr. f. d. ges. exper. Med. **50**:52, 1926.

4. Roger, G. H.; Rathery, F., and Binet, L.: Action du poumon sur le sucre du sang, Compt. rend. Soc. de biol. **90**:1228, 1924.

5. Mauriac, P., and Dumas, R.: Sur la fonction glycolitic du poumon, Compt. rend. Soc. de biol. **90**:1050, 1924.

6. Kosaka, Reiji: Experimental Investigation on the Mechanism of Crisis in Pneumonia, Acta scholae med. univ. Imp. Kioto **8**:341 and 361, 1927.

in the pulmonary alveoli did not cause any apparent harm. He explained this phenomenon on the basis that phenol combines with sulphuric acid which is normally formed within the lungs, thus producing a non-poisonous sulphuric acid ether.

Similarly, bacteria which have been inhaled into the lungs or cellular elements (cancer cells) which have reached these organs by way of the blood stream or otherwise are phagocytosed and largely destroyed in these organs (Büchner,[7] Goldmann,[8] Briscoe[9]). Aschoff[3] stated that megakaryocytes from the bone marrow frequently reach the lungs and there undergo destruction. He quoted the experiments of Simpson, McNee, and Kyiono, who observed a destruction of white cells in the pulmonary parenchyma. Aschoff suggested that, analogous to the spleen which destroys red cells, the lungs may possibly be a "graveyard" for certain groups of white cells. Recent investigations by German workers are to the effect that the lungs are extremely sensitive to various substances introduced by mouth or by way of the blood stream. It was also noted that changes occur in the pulmonary parenchyma in various immunifacient and anaphylactic processes. The lungs, then, are virtually a "barometer" in the bodily economy.

Whereas the rôle of the lungs as a metabolic or antidotal organ is still to be investigated, their rôle as a defensive apparatus has been noted by earlier writers.

The defensive rôle of the organism in general is attributed by recent investigations to the connective tissue and particularly to a variety of cells which in the earliest stages of ontogenesis are derived from the embryonic connective tissue, the mesenchyme. These cells, known as macrophages, clasmatocytes, histiocytes or polyblasts, were originally described by Metchnikoff,[10] who produced evidence that they are concerned only with the defense of the organism: ingesting bacteria (phagocytosis) which have made their way into the body, producing antibodies and forming antitoxins. Particularly has attention been called to the macrophage since the introduction in experimental pathology of supravital staining of animals. Goldmann,[11] on injecting solutions of pyrrol blue into the veins of animals, noted that the dye is taken up

7. Büchner, H.: Untersuchungen über den Durchtritt von Infections-erregern durch die intakte Lungenoberfläche, Arch. f. Hyg. **8**:147, 1888.

8. Goldmann, Edwin: Studien zur Biologie der bösartigen Neubildungen, Beitr. z. klin. Chir. **72**:1, 1911.

9. Briscoe, J. C.: An Experimental Investigation of the Phagocytic Action of Alveolar Cells of the Lungs, J. Path. & Bact. **12**:66, 1908.

10. Metchnikoff, E.: L'immunité dans les maladies infectieuses, Paris, 1901.

11. Goldmann, Edwin: Die äusere und innere Sekretion des gesunden und kranken Organismus im Lichte der "vitalen Färbung," Beitr. z. klin. Chir. **64**: 192, 1909; **78**:1, 1912.

by one variety of cells in a special manner, being deposited in the cellular cytoplasm as fine and coarse granules. The blood cells, the elements of lymphoid or myelogenous origin, remain unstained. He was the first to observe that these cells possessing specific vital-staining peculiarities are found in all parts of the body, including the central nervous system;[12] and, according to their affinity for the vital dye, he called them "Pyrrholzellen" (pyrrol cells). He identified the pyrrol cells with the clasmatocyte which Ranvier[13] found abundantly in the milky spots (*taches laiteuses*) of the omentum.

The original conception of Metchnikoff, who attributed to the macrophage defensive potentialities only, has recently been immensely broadened. Today one attributes to the mesenchyme, and particularly to the macrophage, a dominating rôle in the formation of bile and also in the metabolism of various substances, such as water, lipoids, iron, cholesterol, etc. The connective tissue is believed to be not only a "frame"—that is, a silent supporting substance—but an "organ," endowed with various highly differentiated functions and, analogous to glands, possessing possibly the properties of internal secretion.

The lungs are the single visceral organ which is in direct contact with the outside world. They are therefore liable to receive directly from the air dust, bacteria and other particulate matter. From a circulatory point of view, they are the point of convergence of the body, and material which happens to invade the blood or lymph streams invariably reaches the lungs.

For decades discussions were centered around the character of the cellular response of the lungs in inflammatory and congestive processes and also around the source of these cellular elements. The problem, which appears at first to be merely one of cytology, is in reality one of the pulmonary mesenchyme and its potentialities; that is, of its physiopathology. In general, two possibilities were considered: (1) that the lungs are apparently deprived of any defensive mechanism of their own, and that the "reactive" cells found in the alveoli are brought to the pulmonary field by way of the blood stream; (2) that they are produced locally.

As said before, Goldmann[11] established the fact of the ubiquity of the pyrrol cell (macrophage) possessing specific vital-staining peculiarities. From this observation as a point of departure has come the idea of studying the pulmonary reactions to vital dyes, on the assumption that if the lungs harbor "indigenous" macrophages (histiocytes) they ought to be marked by the dye and thus be identifiable.

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12. Goldmann, Edwin: Vitalfärbung am Zentralnervensystem, Abhandlung der K. P. Akad. d. Wissenschaften, Berlin, 1913.

13. Ranvier, L.: Des clasmatocytes, Arch. d'anat. micr. **3**:122, 1900.

But even with the use of this biologic test, there was and still is a lack of agreement on the part of different observers.

To elucidate the problem, the following methods were employed: (1) intravenous and intratracheal injections of vital dyes into laboratory animals and (2) intratracheal injection of oils.

EXPERIMENTS

Experiments with Use of Intravenous and Intratracheal Injections of Vital Dyes.[14]—The first series of experiments was conducted on rabbits, guinea-pigs and white rats, which received one or many injections of a sterile solution of 1 per cent of pyrrol blue into the veins or into the peritoneal cavity.

In examining the tissues of the vitally stained animals, it was noted that the repeatedly injected dye, while staining very deeply the viscera, pelvic organs and genitalia of the animals, had stained the lung to a slight degree only. Under the microscope, the cells of the histiocytic group (reticulo-endothelial or macrophage system) were abundantly stained in the liver, spleen and other abdominal viscera. In the lungs, the dye was often stored in the adventitial cells (macrophages) of the larger vessels, faintly in the vascular intima and media, and here and there in large cells seen in the interalveolar septums. Judged by their morphology and also by the fashion in which the dye is distributed in their cellular cytoplasm, these cells were beyond doubt macrophages. The other pulmonary structures remained unstained.

Similar observations have previously been made by writers, who assumed that the liver had taken up the bulk of the dye, which consequently reached the lungs in an insignificant amount. Sewell[15] and Westhues[16] reached the conclusion from similar experiments that the cells of the histiocyte group were scanty in the lungs. It occurred to me that the scantiness with which the pulmonary tissue was stained when the dye had been introduced by way of the veins or peritoneum might be due to a number of factors: (1) The Kupffer cells of the liver might have retained the dye and thus acted as a barricade, in which the polygonal hepatic cells themselves might have also played some rôle though a nonspecific one; (2) the dye became greatly diluted when given by intravenous or intraperitoneal injection, thus losing its power of irritating the receptive pulmonary cells; (3) a large part of the injected material was excreted through the kidneys and the gastro-intestinal tract.

It was thought, consequently, that the amount of dye that reached the lung was probably insufficient to call forth the macrophages, and to conclude from the foregoing experiments that the lungs are actually poor in histiocytes seemed premature. Accordingly, it was determined to inject the dye intratracheally, and to study the effects of its direct application to the lung.

When the animals were stained in this way, the following picture was observed. In the first place, there was an increase in the cellular elements of the alveolar septums. In numerous instances, the cells proliferated to such an extent as to obliterate the normal pulmonary structure. Some of the cells had increased in size,

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14. Fried, B. M.: The Origin of Histiocytes (Macrophages) in the Lungs, Arch. Path. **3**:751 (May) 1927.

15. Sewell, W. T.: The Phagocytic Properties of the Alveolar Cells of the Lungs, J. Path. & Bact. **22**:40, 1918-1919.

16. Westhues, H.: Herkunf der Phagocyten in der Lunge, Beitr. z. Path. Anat. u. z. allg. Pathol. **70**:221, 1922.

appearing as swollen cells with a foamy cytoplasm. Frequently the cells contained granules of dye, which were distributed in the cytoplasm just as granules are distributed in macrophages.

Of particular interest were the cells lining the air sacs. They had enlarged; their cytoplasm, which had become abundant and "foamy," contained droplets of

Fig. 1.—A section of rabbit's lung after intratracheal injection of pyrrol blue. It shows an area of proliferation of the cells lining the alveoli under the influence of the vital dye. The dye is seen in the cellular cytoplasm as coarse and fine black granules. The cells are typical macrophages. In the left upper quadrant they are seen attached to the alveolar wall.

pyrrol blue distributed in a histiocytic manner. It seemed certain that the "tatooed" cells had detached themselves from the septums, thus forming essentially the interalveolar exudate. The capillary endothelium did not show any cytopoietic properties.

Summary: Intratracheal injections of vital dyes stain the cells commonly designated as respiratory epithelium in a way which resembles closely the staining of the macrophages. These cells "irritated" by the phagocytosed dye undergo morphologic changes, proliferate instantaneously, and detach themselves from the alveolar wall to form the intra-alveolar exudate ("dust cells," "wandering macrophages").

Experiments with Use of Intratracheal Injections of Oils.—Rabbits and cats were used in these experiments. The trachea of the animal was exposed in a manner previously described.[17] Three cubic centimeters of iodized oil 40 per cent,[18] of cod liver oil (oleum jecoris aselli) or of liquid petrolatum, respectively, heated to body temperature, was then injected into the lungs via the trachea, and the animals were killed at different intervals following the injections. Tissues were fixed in a solution of 10 per cent formaldehyde and stained with hematoxylin and eosin and with different silver nitrate methods. Frozen sections were stained with Herxheimer's stain for fat, with Giemsa's stain, and with silver tannin methods.

When the lungs were removed and examined about one hour after the injection of the oil, there was noticed under the microscope a diffuse increase in "nuclei" scattered all over the sections. These gave the impression at first of being endothelial cells lining the pulmonary capillaries. But close investigation revealed the following: The capillary endothelium was as usual flat and elongated, having its convex surface toward the vascular lumen, whereas the "nuclei," being larger and plumper, lay either astride the capillary wall or outside of it. Moreover, they were not separated by roughly equal distances from each other as the endothelial cells often are, but were gathered in groups, being "stronger" at one or another point. Investigated with high power lenses, these cells revealed a cytoplasm which contained vacuoles of varied sizes and a hyperchromatic round and oval nucleus. They protruded above the surface of the alveolar wall in a bud-like manner. This in a somewhat exaggerated form can be seen in figure 2.

Small cells, similar to those lining the wall, containing occasional drops of oil, could be found here and there free in the alveolar lumen. Within twenty-four hours following the injection, the alveolar wall cells showed a marked increase in number and also in size (large, foamy cells) leading to thickening of the alveolar septums (figs. 2, 4 and 5).

The reaction went on crescendo with each subsequent hour. At the end of the second and third days, the cellular proliferation led to small atelectatic areas. In places, the swollen foamy cells lining the septums and those accumulated in the pulmonary alveoli produced continuous cellular masses (figs. 2 and 5).

The proliferated cells formed giant cells of the Langhans type. Figure 6 shows two stages of the giant cell formation. In figure 6, *A* (first stage) individual cells of which the giant cell is made up are distinct. The identity of these cells with those of the septums is beyong doubt. One sees moreover the cellular syncytium growing out from the cells of the alveolar wall. In figure 6, *B* (final stage), the multinucleated cells bear all the landmarks of a fully developed giant cell of Langhan's type.

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17. Fried, B. M., and Proctor, E. E.: The Appearance of Specific Antibodies in the Serum of Rabbits by Intratracheal and Intravenous Injections of Living Tubercle Bacilli, Proc. Soc. Exper. Biol. & Med. **21**:396, 1924.

18. Fried, B. M., and Whitaker, L. R.: Intratracheal Injection of Iodized Oil; Experimental Studies, Arch. Int. Med. **40**:726 (Nov.) 1927.

The reaction of the cells, being equal qualitatively toward cod liver oil and liquid petrolatum, showed, however, the following differences. In the first place, cod liver oil was readily phagocytosed, when the amount of injected oil was moderate, while liquid petrolatum was almost untouched. In the second place, the cells took on somewhat different aspects depending on the kind of oil used. Figures 2 and 4 show the morphology of the pulmonary cells of a cat treated with cod liver oil. Figure 5 is taken from a section of the lung of a rabbit that received, intratra-

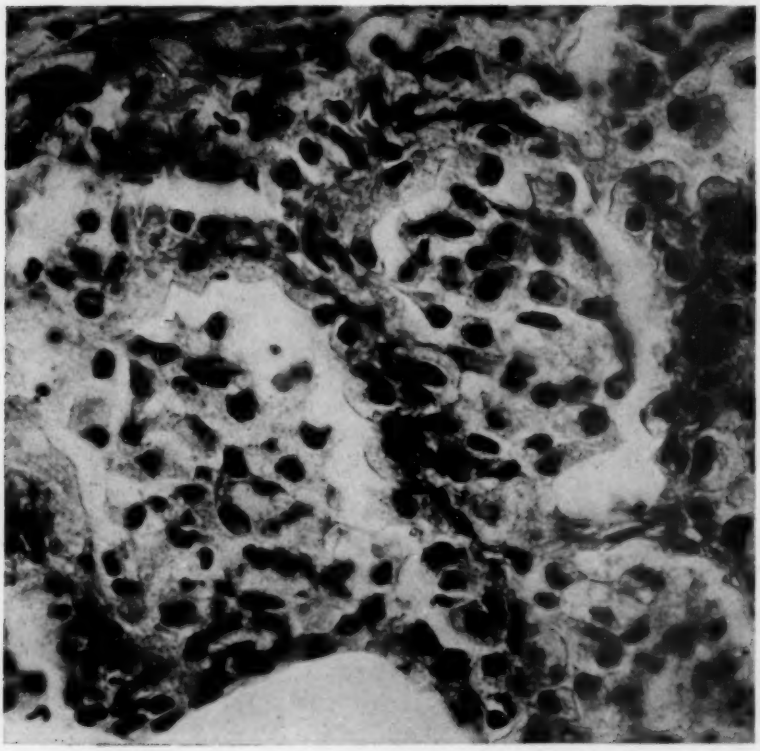

Fig. 2.—A section of cat's lung following intratracheal injection of cod liver oil. The alveoli are filled with large "foam" cells, which are macrophages. The cells are in direct continuation with those lining the alveolar septum, which they closely resemble. Free macrophages may also be noticed. Hematoxylin and eosin; × 600.

cheally, liquid petrolatum. It is also noteworthy that liquid petrolatum called forth quite numerous mitoses, whereas with the cod liver oil mitotic figures were of rare occurrence.

The reaction of the lymphoid tissue was also much more intense with liquid petrolatum than with cod liver oil.

The endothelium of the septal capillaries showed a slight swelling, but no proliferation.

Summary: Small amounts of oils injected into animals' lungs by way of the trachea cause a reaction confined essentially to the cells lining the wall of the alveoli. These cells "swell," acquire a foamy cytoplasm, proliferate instantaneously, phagocytose the oil, and finally detach themselves from the pulmonary septums to form the "inflammatory" intra-alveolar exudate. They also form giant cells of the Langhans type.

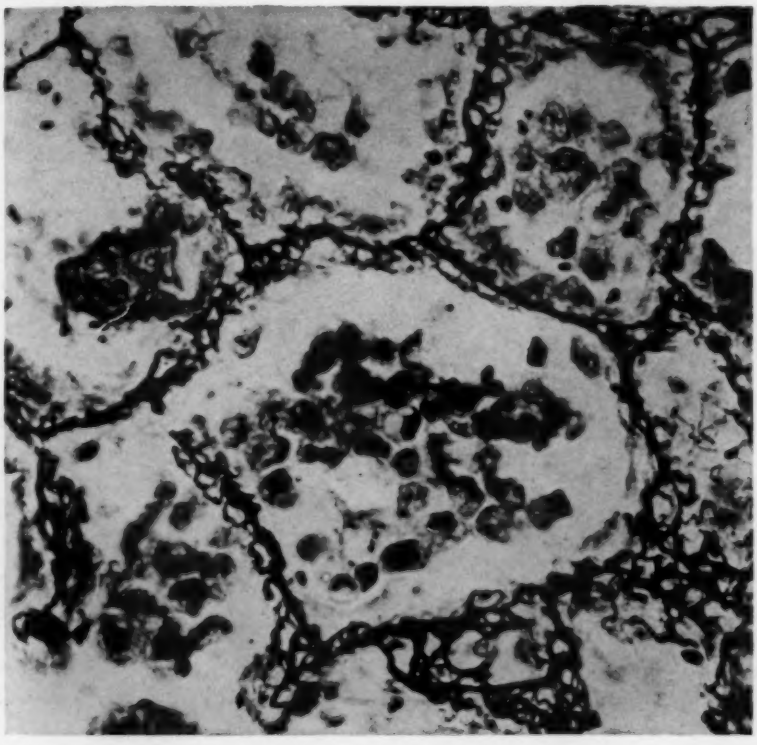

Fig. 3.—A section of cat's lung following intratracheal injection of cod liver oil. It was stained by Perdrau's silver nitrate method. The alveoli contain macrophages. "Ghosts" of the same cells are seen along the alveolar wall. There is no epithelium lining the septums; × 600.

INTERPRETATION OF EXPERIMENTS

The monistic conception of the pyrrholzelle brought forward by Goldmann [11] underlies as a cornerstone numerous most noteworthy problems in experimental pathology, and has for a decade. Aschoff [19] was first to identify Goldmann's pyrrol cell with Metchnikoff's macro-

19. Aschoff, L.: Das Reticulo-endotheliale System, Ergebn. d. inn. Med. u. Kinderh. **26**:1, 1924.

phage, and, in consideration of the physiologic properties common to this particular group of cells, he aptly included them in his reticulo-endothelial defensive and metabolic apparatus. Following Aschoff's publication, Anitschkow [20] found that the "histiogenous macrophages" phagocytose and store lipoid substances; that is, they are also "cholesterinphagocytes."

The presence of fat droplets in the cytoplasm of the macrophage was noted by earlier writers. Waldeyer [21] was probably the first to attribute

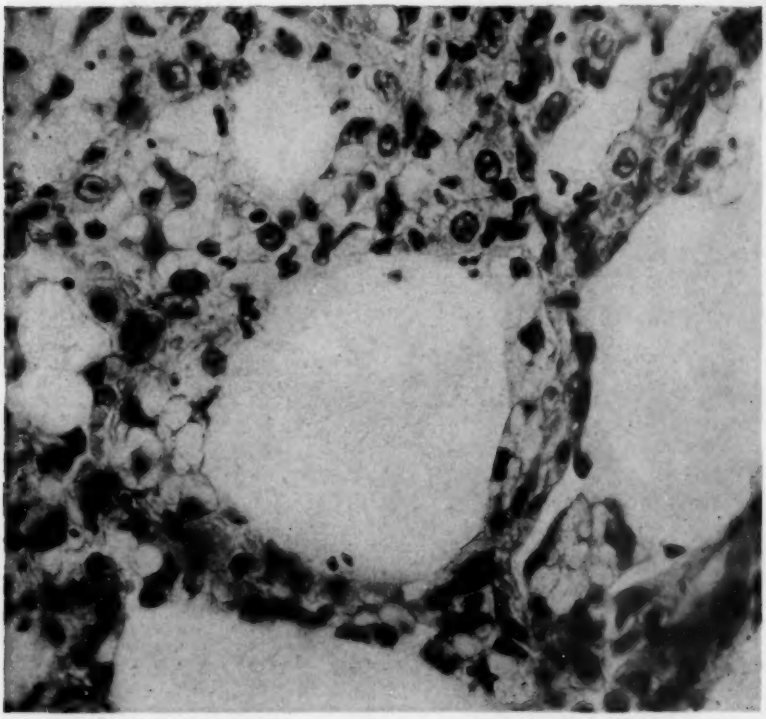

Fig. 4.—A section of cat's lung following intratracheal injection of cod liver oil. The cells lining the alveoli are "transformed" into fat cells. The alveolus is surrounded by proliferated masses of similar cells. In the right upper quadrant is seen a section of a septum with attached cells at different stages of "transformation." Hematoxylin and eosin were used; × 600.

to what he called the "embryonic cells of the connective tissue" or "plasmazellen" the avidity for fat (die grosse runde Zellen welche besonders gern Fett aufnehmen). François,[22] too, noticed that these

20. Anitschkow, N.: Ueber experimentell erzeugte Ablagerungen von Anisotropen Lipoidsubstanzen in der Milz und im Knochenmark, Beitr. z. Path. Anat. u. z. allg. Pathol. **57**:201, 1913-1914.

21. Waldeyer, W.: Ueber Bindgewebszellen, Arch. f. mikr. Anat. **11**:176, 1875.

cells possess the property of becoming "transformed" into fat cells. But these isolated observations passed unnoticed, and the presence of lipoids in the macrophage was regarded by many as being due to a diseased condition of the cell.

Maximow,[23] however, affirmed that the inclusion of droplets of fat within the cytoplasm of the polyblast (macrophage) is a physiologic metabolic process characteristic of the cells. Years later Anitschkow [24]

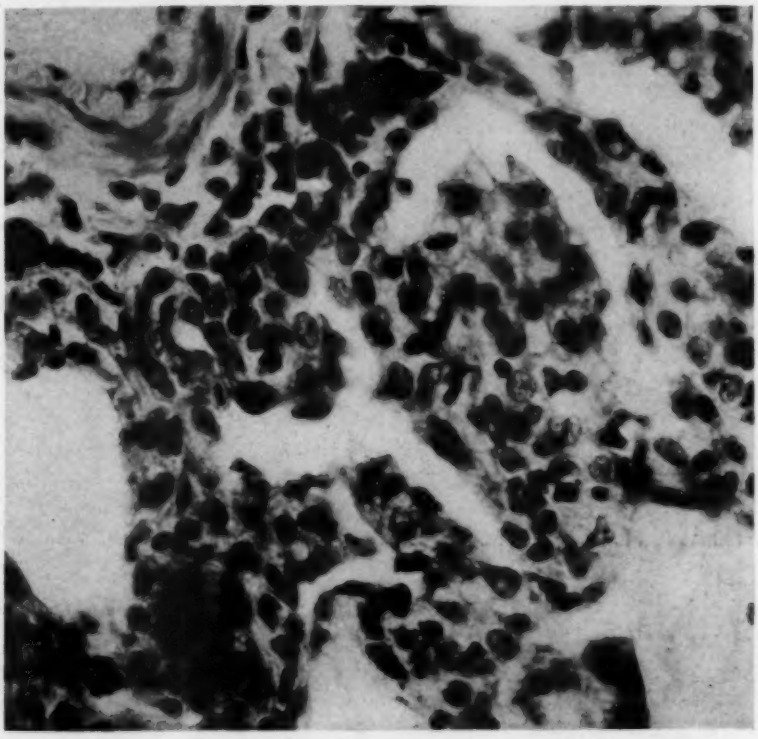

Fig. 5.—A section of rabbit's lung following intratracheal injection of liquid petrolatum. It shows heavy proliferation of the alveolar wall cells. One alveolus is almost occluded by masses of cells. A similar crowding of macrophages is possibly a prelude to their transformation into fibroblasts. The mitotic figure must be noticed. Hematoxylin and eosin were used; × 600.

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22. François, P.: Recherches sur le developpment des vesseaux et du sang dans le grand epiploon du lapin, Arch. de. biol. **13**:521, 1895.

23. Maximow, A.: Experimentelle Untersuchungen über die entzündliche Neubildung von Bindgewebe, Beitr. z. Path. Anat. u. z. allg. Pathol. **5**:1, 1902.

24. Anitschkow, N.: Ueber die Atherosklerose der Aorta beim kaninchen und ueber deren Entstehungsbedingungen, Beitr. z. Path. Anat. u. z. allg. Pathol. **59**: 306. 1917.

found that laboratory animals, overfed with cholesterol emulsified in sunflower oil, show in the intima of their vessels large cells studded with lipoids, which he readily identified as macrophages; in another series of investigations,[20] he found that rabbits fed in excess with pure cholesterol or with the yolk of egg reveal an amazing storage of the lipoid substances

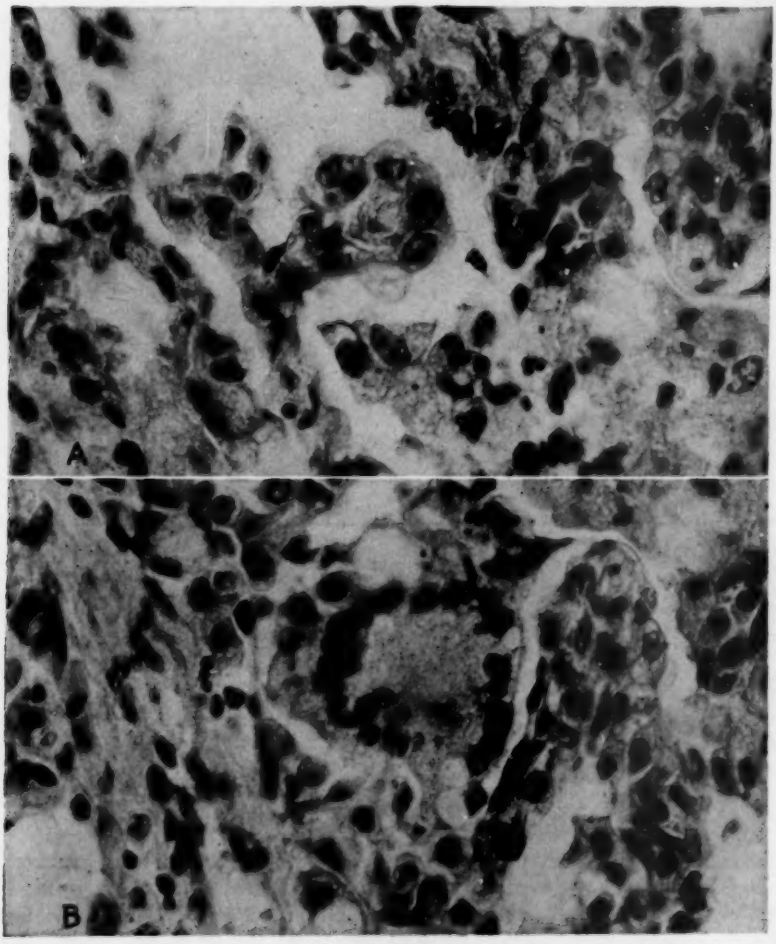

Fig. 6.—A section of cat's lung following intratracheal injection of cod liver oil. In *A*, there is apparently an early stage of giant cell formation. The multinucleated cell originated from the cells lining the wall of the alveoli. In *B*, the giant cell is of Langhans' type. It also originated from the alveolar wall cells, and is built from the fusion of many cells and not by nuclear division of one cell. Hematoxylin and eosin were used; × 600.

in the spleen and the bone marrow. Microscopic examination of these organs revealed that the material is deposited exclusively in the reticular and the specific endothelial cells of the sinuses. Under the influence of

the excessive feeding of cholesterol, these cells enlarge and proliferate, forming wide agglomerations in the splenic pulp and also in the sinuses. In the bone marrow, the orally introduced fatty substance led to cellular changes similar to those found in the spleen. Anitschkow [25] further noted that cholesterol artifically increased in the organism is largely deposited as anisotropic fat in the macrophages of the connective tissue forming typical xanthoma cells. Zinserling's [26] more recent experiments are in complete accord with those of Anitschkow. He found that the oral and parenteral administration of cholesterol calls forth essentially a macrophage reaction. It is noteworthy that the rapidity with which the large phagocytes respond to the lipoid varies from organ to organ. Thus when introduced by mouth, the Kupffer cells and those of the bone marrow phagocytose the lipoids earlier than do the splenic and lymph node macrophages. On the other hand, the Kupffer cells require much more fat to "round off," whereas reticular and "littoral" cells of the spleen "swell" and proliferate from the slightest excess of the lipoid material. In the spleen itself, the "littoral" cells take up the lipoids much earlier than do the reticular cells.

In man, too, an excess of lipoid in the blood leads to changes in some visceral organs similar to those found experimentally in animals. In lipemia due to diabetes, nephrosis, and obstructive jaundice, the macrophages and particularly those of the spleen display peculiarities analogous to those found in the rabbit overfed with cholesterol. Oppenheim and Fishberg [27] and Warren and Root [28] reported cases of lipemia in diabetic patients. In these cases, the entire splenic pulp was made up of large "foam" cells (reticulo-endothelial) which were similar to those produced experimentally by Anitschkow. It is interesting that the Kupffer cells showing the presence of droplets of fat, revealed by special stains, did not present the striking foamy appearance found in the reticulum cells of the spleen, nor did they proliferate.

In brief, then, the macrophage is the cell par excellence which attacks the lipoids introduced experimentally or which have flooded the organism as a consequence of faulty metabolism of fats within the body itself (lipemia).

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25. Anitschkow, N.: Experimentelle Untersuchungen über die Ablagerung von Cholesterinfetten im subcutanen Bindgewebe, Arch. f. Dermat. u. Syph. **120**:627, 1914.

26. Zinserling, W.: Ueber die Anfangsstadien der experimentellen Cholesterin Verfettung, Beitr. z. Path. Anat. u. z. allg. Pathol. **71**:292, 1923.

27. Oppenheim, H. S., and Fishberg, Arthur M.: Lipemia and the Reticulo-Endothelial Apparatus, Arch. Int. Med. **36**:667 (Nov.) 1925.

28. Warren, S., and Root, H. F.: Lipoid-Containing Cells in the Spleen in Diabetes with Lipemia, Am. J. Path. **2**:69, 1926.

Apparently the pulmonary reaction called forth in my experiments with the intratracheal injection of oil is of the same histiocytic type.

A priori it is improbable that the reaction of the lungs to lipoids introduced from without should differ from that of the spleen or the bone marrow. In tuberculosis, as is well known, the pulmonary response to Koch's bacillus is identical with that of other tissues. Furthermore, as seen from the experiments herein presented, oil and vital dye respectively are attacked by one and the same group of cells, being stored in their cytoplasm in a similar manner.

On the basis, therefore, of the morphologic and physiologic analogies (storage of vital dyes and lipoids) between the alveolar phagocytes and those found in the spleen and the bone marrow, it is safe to conclude that they belong to the same family; that is, they all are histiocytes or macrophages.

The question arises as to their source in the lungs. The different theories as to the local or hematogenous origin of alveolar macrophages have been discussed in a previous study based on the use of vital stains.[14] Today the opinion is almost unanimous that the cells are produced locally (Maximow,[29] Lang,[30] Bloom,[31] Gardner and Smith [32]). It appears, moreover, certain that in the experiments herein reported with the use of oils, as in those with the use of vital dyes, the cellular exudate originates from the cells lining the wall of the air sac, which are not other than "indigenous" macrophages in a resting state. As in the experiments with pyrrol blue, the oil is almost instantaneously attacked by the cells "lining" the wall of the pulmonary alveoli. The difference is only in the intensity and possibly to some degree in the promptness of the pulmonary reaction called forth by the two substances respectively. Lipoids are possibly a more "attractive" and more powerful antigen for the pulmonary phagocyte than the dye. One single intratracheal injection of from 2 to 3 cc. of this substance leads to a perturbation of the entire pulmonary mesenchyme with the instantaneous mobilization of all its resting elements.

The importance of the antigen in the evaluation of the phagocytic potentialities of the macrophage cannot be overemphasized. Still Metchnikoff [10] noted that in many cases the macrophages ought to be

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29. Maximow, A.: Morphology of the Mesenchymal Reactions, Arch. Path. **4**:557 (Oct.) 1927.

30. Lang, F. J.: Ueber Gewebskulturen der Lunge, Arch. f. Zellforsch. **2**:93, 1926.

31. Bloom, William: Immune Reactions in Tissue Culture, I. Arch. Path. **3**: 608 (April) 1927.

32. Gardner, L. U., and Smith, D. T.: The Origin of the Alveolar Phagocytes Studied in Paraffin Sections of Tissue Stained Supravitally with Neutral Red, Am. J. Path. **3**:445, 1927.

"trained" for the performance of their duty (un perfectionnement des phagocytes á digérer leur proie), while in others they are driven altogether away from their supposed "prey." Bloom,[31] in recent studies, observed that when pigeon's erythrocytes are added to cultures of normal rabbit lung, the red cells remain untouched. But when the same cells are added to cultures from lung tissue immunized against these cells, the erythrocytes are largely phagocytosed.

Lipoids, then, injected into the lungs by way of the trachea, affect primarily and essentially the cells "lining" the wall of air sacs. These cells, which are barely visible in normal sections of lungs, hypertrophy, phagocytose the oil, and store it in their cytoplasm as fine and coarse granules. Moreover, they promptly proliferate, detach (desquamate) themselves from the alveolar wall and lie free in the alveolar lumen, where they continue their wandering phagocytic activities. In a word, their behavior and also their morphology are exactly like that of the "cholesterinphagocyten" found by Anitschkow [33] and others in the spleen and the bone marrow and identified by them as "histiogenous macrophages" (figs. 2 and 7).

An additional proof from the experiments reported that the alveolar wall cells are resting macrophages is their ability to form giant cells of the Langhans type. Giant cells found in tissues in pathologic conditions are commonly grouped into the "foreign body" and the Langhans type varieties. The former is characterized by an irregular dissemination of the nuclei throughout the cytoplasm; the latter is remarkable in that its nuclei are arranged in a horseshoe manner at the cellular border. These multinucleated cells are thought to be formed under the influence of some injurious or irritating substance (usually the tubercle bacillus) which comes in contact with the pluripotential mesenchymal cells affecting "the whole cell, its interior as well as its surface" (Lewis).[34]

The intimate process of the cellular changes leading to the formation of giant cells is unknown. Moreover, it is still a matter of discussion whether the multinucleated cells are formed through fusion of individual cells or following division of the nucleus of one cell. Lang in his studies of lung cultures inoculated with tubercle bacilli failed to disclose the presence of giant cells of the Langhans type so characteristic of tuberculosis. A photomicrograph of a section of a lung from a cat that was treated with cod liver oil in a manner indicated is shown in figure 6. The physiognomy of the cells seen in this picture is characteristic of the macrophage, and the intimate relationship between these cells and those of the wall of the air sac is obvious. The interest, however, lies in the

33. Anitschkow (footnotes 20 and 25).

34. Lewis, Warren H.: Formation of Giant Cells, Am. Rev. Tuberc. **8**:317, 1927.

presence of giant cells. In figure 6, *A*, the early stage of the formation of giant cells is shown. The polynuclear cell here is made up of several isolated cells, the boundaries of which can readily be made out. In figure 6, *B*, one sees a typical giant cell of Langhans' type similar to that found in tuberculosis, in which it is made up of epithelioid cells. A careful inspection of this picture will reveal the presence of faint boundaries

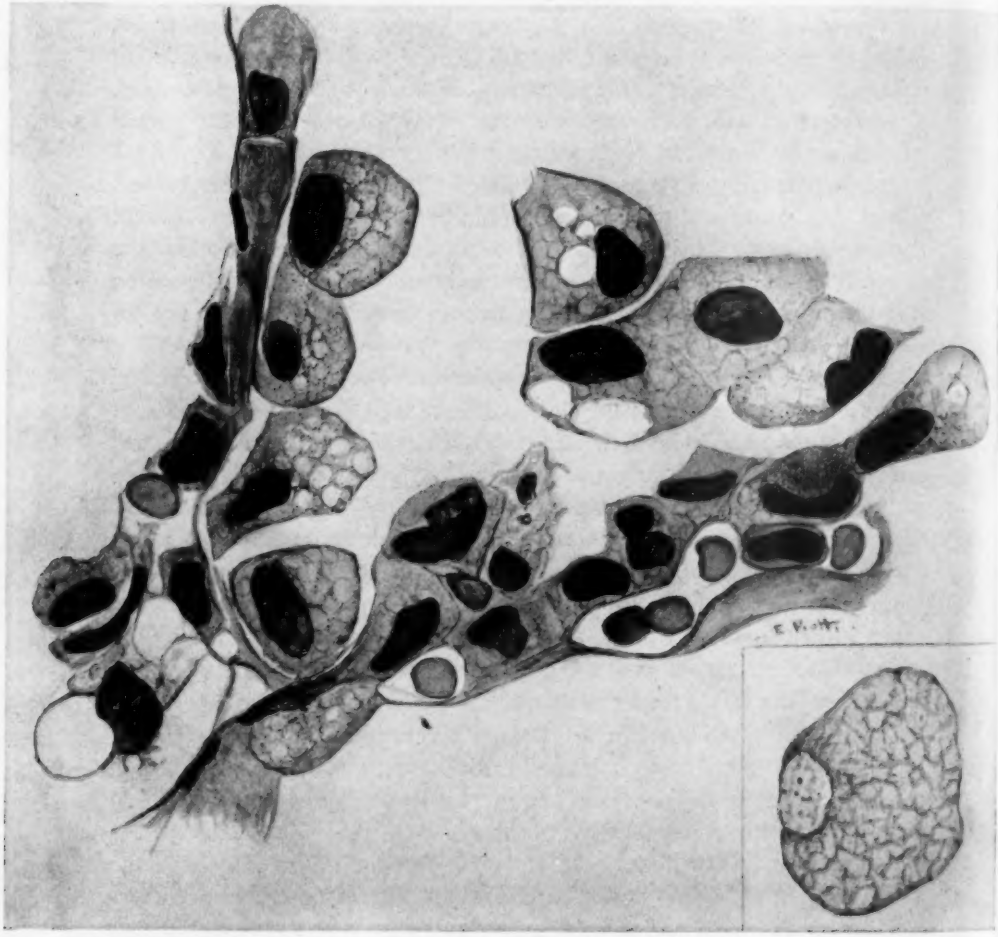

Fig. 7.—A drawing showing a "corner" from a pulmonary alveolus (cat's lung; compare fig. 2) following intratracheal injection of cod liver oil. The large "foam" cells are macrophages. In the left side of the picture they are "caught" while separating from the alveolar septum. The fixed and the free interalveolar macrophages closely resemble each other; × 2000.

In the insert is a hypertrophied "cholesterol phagocyte" found to be partly detached from the wall of the blood sinus of the spleen.

in the cytoplasm marking the confines of individual cells. It seems therefore certain that the multinucleated cell in this case is formed by fusion of many individual cells and not by the nuclear division of one particular cell. It is accepted that giant cells of this variety when found in the lungs are formed from the so-called "dust cells," which, as already stated, are histiocytes originating from the cells "lining" the wall of the alveoli.

This, then, once more favors the conception of the mesenchymal origin of the cells lining the walls of the air sacs erroneously designated as alveolar "epithelium."

CLINICOPATHOLOGIC OBSERVATIONS

Pagel,[35] in studying the origin of macrophages in experimental tuberculous pneumonia, found that in the guinea-pig these cells are tinctorially similar to those lining the wall of the alveoli. But the same staining methods applied to human material failed to disclose analogies between the fixed and the wandering cell. This is possibly due to the fact that the experimental material was fresh and the difference between the two cells had not entirely disappeared, whereas in human tissues, fixed many hours after death, profound changes might have occurred in the cells serving to efface deeply the fine structural analogies between the mother and daughter cells. Even more, in recently obtained experimental tissues, Gardner and Smith [32] found differences between the sessile and the free cell. In studies on human lungs, I have observed that striking similarities between the two cells can be found even in the customary hematoxylin and eosin sections, as the following examples will show.

Example 1 (fig. 8).—The lung showed a tuberculous caseated area about 1 cm. in diameter surrounded by a dense fibrous capsule. There also was present a nontuberculous bronchopneumonia. The photomicrograph was taken from an area remote from the advanced pathologic changes just mentioned. Here there were emphysematous distortion of the alveoli, edema and congestion. The pulmonary reaction was confined to the cells lining the alveoli, which showed swelling, vacuolization of cytoplasm, proliferation and desquamation into the alveolar lumen. The interest of figure 8 is twofold: In the first place, there is the striking similarity between some of the fixed and the wandering cells; in the second place, there is a dissimilarity between the fixed septal cells themselves. It is safe, however, to assume that all these cells are of the same parentage and that they are to all appearances, macrophages.

In the left part of the picture, there is a "dust cell" loaded with granules, a couple of macrophages, serum, red cells and a few shreds of fibrin.

Example 2 (fig. 9).—The case was that of an aleukemic lymphadenosis in a girl 17 years old. The lung did not show signs of pneumonia, but the alveoli revealed the presence of fibrin, red cells and serum. This was confined to rather

35. Pagel, W.: Zur Frage der Abstammung der Exudatzellen bei Käsiger Pneumonie, Beitr. z. klin. d. Tuberk. **61**:221, 1925.

sharply localized areas. As in the foregoing example, the cells lining the septums showed the most prominent reaction. Although the picture here is not as clearly cut as in other examples, it is nevertheless convincing as to the nonepithelial nature of the alveolar lining and also as to the fixed and wandering cells' being identical. Sections taken from different parts of the lungs showed also small lymphocytes with a hazy, patchy cytoplasm at different stages of transformation into large phagocytic cells. Maximow and his assistant (Bloom[36]) have produced evidence to show that the small lymphocyte may under certain conditions be transformed into

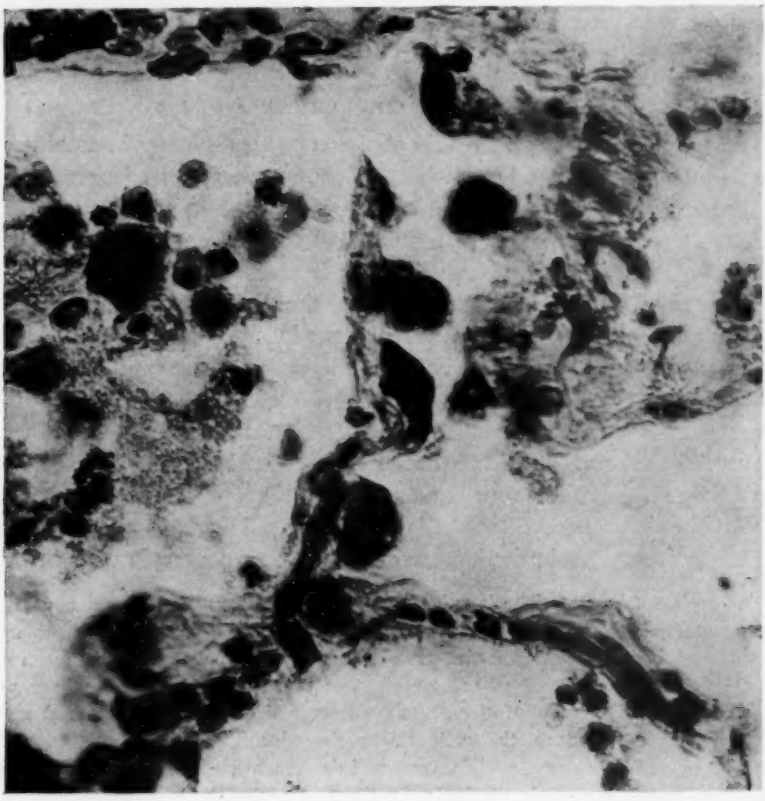

Fig. 8.—A "corner" from a pulmonary alveolus in the human lung, showing the sessile and free alveolar cells. The four cells along the wall of the alveoli show different stages of their development from flat endothelioid to large epithelioid cells. The similarity between the second cell (from above) and the free cell to its right must be noted. The alveolus to the left contains a few macrophages, one of which represents a typical "dust cell." Methylene blue and eosin were used; × 700.

36. Bloom, W.: Ueber die Verwandlung der Lymphozyten der Lymphe des Ductus thoracicus des Kaninchens in Polyblasten (Makrophagen) in Gewebskulturen, Centralbl. f. allg. Pathol. u. path. Anat. **39**:3, 1927.

a macrophage. Human material that I have studied seems in many instances to suggest a similar metamorphosis.

Example 3 (fig. 10).—This was a case of primary bronchiogenic cancer. In the part of the lungs free from tumor there were emphysema, edema and congestion. The reaction was essentially that of the cells lining the wall of the alveoli. Here again there are close similarities between the fixed (alveolar wall) and the wandering cell (exudate).

Summary.—In the examples from human material, it appears that: (1) the pulmonary alveoli are not lined in a syncytium-like manner by

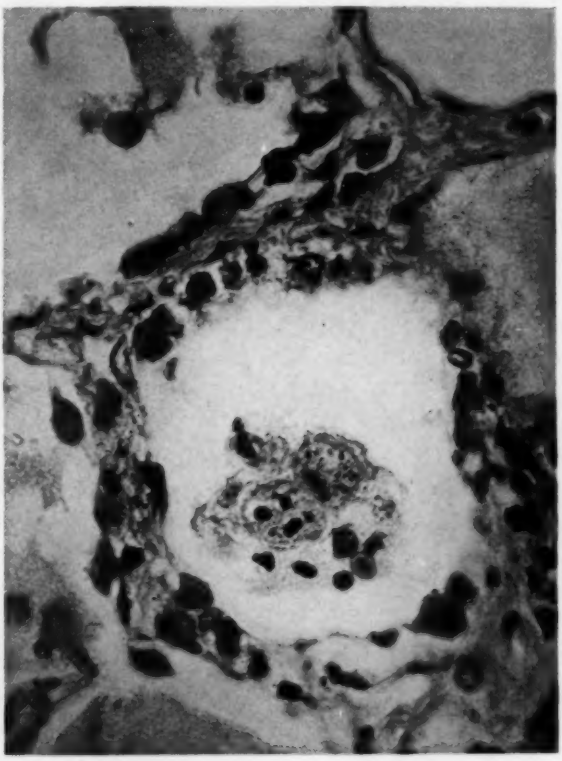

Fig. 9.—Section of human lung showing swelling and proliferation of the cells alongside the alveolar wall. The alveolar lumen contains a group of "dust cells."

epithelial cells; (2) the pulmonary reaction is confined to the cells found in groups along the wall of the alveolar septums, which under the influence of different stimuli enlarge, proliferate and abandon their seat to escape in the alveolar lumen; (3) the fixed and the wandering alveolar cells frequently resemble each other and display all the characteristics proper to "histiogenous macrophages."

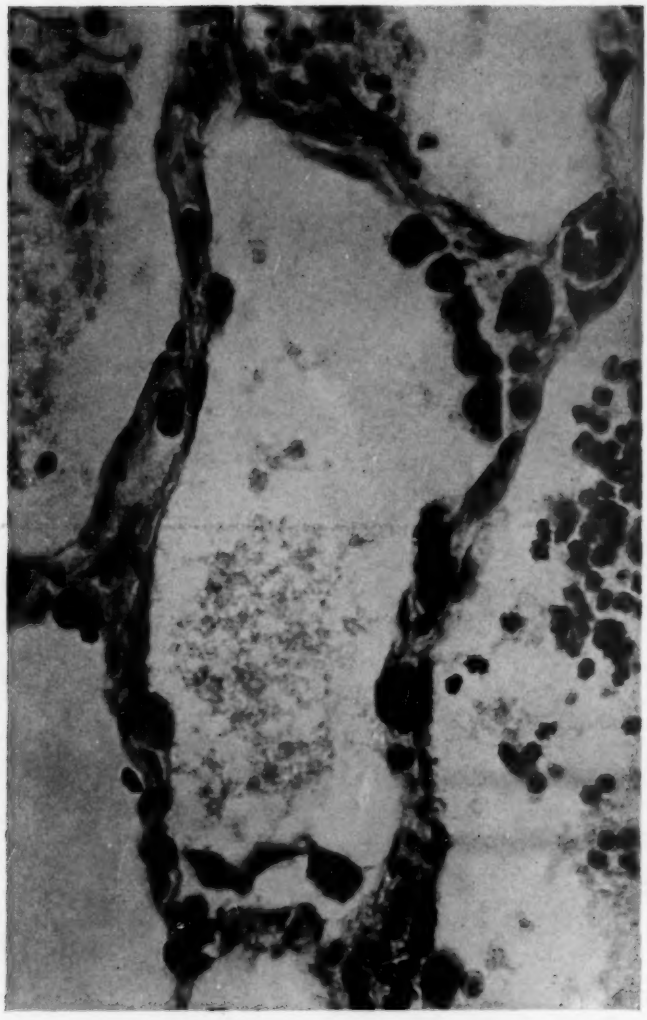

Fig. 10.—Section of human lung taken from a distended pulmonary alveolus. The fixed cells along the alveolar septum (right upper quadrant) and those lying free in the alveoli have the same aspect. Both are to all appearances "histiogenous macrophages." Methylene blue and eosin were used; × 600.

COMMENT

The problem discussed, as it stands today, is considerably simplified as the result of recent experimental studies. In the first place, it is almost unanimously accepted that the lungs abound in histiocytes, and that the local histiocytic mechanism acts with amazing promptness characteristic of this cellular group. In the second place, the conception that the capillary endothelium of the septums is the progenitor of the pulmonary macrophage is abandoned even by its most persistent advocates (Foot [37]). Apparently, the cells lining the alveolar wall commonly designated as respiratory epithelium have no "rivals" in the claim that they give birth to the "dust cells."

The cells which line the wall of the air sacs have been found by every observer to possess peculiarities not proper to epithelium in general. Granel [38] outlined their richness in lipoids and in mitochondria, and compared them with glandular cells. Fauré-Fremiet [39] emphasized their abundance of fat and iron. Seemann,[40] in the laboratories of Aschoff and Tschistovitch, respectively, noted that similar to the peribronchial and perivascular histiocytes the "alveolar epithelium" stores fat and iron and contains crystals. Gerlach and Finkeldey [41] stated that the conduct of the cells of the alveolar wall does not agree with an epithelial origin. Gardner and Smith [32] found that the alveolar septum is lined by epithelial cells and histiocytes, the latter giving rise to the free, wandering macrophage. Lang,[30] and Bloom,[31] from studies with cultures of lung tissue inoculated with tubercle bacilli and pigeon's erythrocytes, respectively, emphatically state that the cells lining the wall of the alveoli (septal cells) are histiocytes. Guieysse-Pelissier,[42] although believing that the septal cells are of endodermal origin, admitted that they behave like histiocytes. "Nous aimons mieux," he said, "continuer à admettre qu'elle (the alveolar epithelial cell) est bien d'origine endodermique, mais nous reconnaissons qu'elle se comporte comme les cellules reticulo-endotheliales." (We would prefer to con-

37. Foot, N. C.: Studies on Endothelial Reactions, Am. J. Path. **3**:713, 1927.

38. Granel, F.: Sur l'elaboration de la graisse dans l'épithelium pulmonaire, Compt. rend. Soc. de biol. **82**:1320, 1919.

39. Fauré-Fremiet, E.: A propos de cellules á graisses de lavéole pulmonaire, Compt. rend. Soc. de biol. **83**:11, 1920.

40. Seemann, G.: Weitere experimentelle Untersuchungen zur Biologie des Lungengewebe und über die mesenchymalen Abwehrvorgänge in Allgemeinen, Beitr. z. Path. Anat. u. z. allg. Pathol. **78**:526, 1927.

41. Gerlach, W., and Finkeldey, W.: Zur Frage mesenchymaler Reaktionen. I. Die morphologisch fassbaren, biologischen Abwehrvorgänge in der Lunge normergischer und hyperergischer Tiere, Krankheitsforschung **4**:29, 1927.

42. Guieysse-Pelissier, A.: L'organ lymphoide du poumon, Arch. d'anat. micr. **23**:347, 1927.

tinue to admit that it [the alveolar epithelial cell] is indeed of endodermal origin, but we recognize that it behaves in the same manner as the reticulo-endothelial cells.) He based his belief on embryologic evidences. In this connection, the opinion of Virchow [43] is pertinent. He wrote: "I shall not lay much stress upon the fact that the doctrine of the embryologic leaflets is not yet clearly elucidated in all its details and that every new investigation along this line brings some modifications. I cannot, however, admit that embryology particularly in its histologic part should be imperative to the pathologist. Here only experiment counts." [44]

Indeed, experimental pathology lacks irrefutable methods of isolation of one particular cell for the purpose of its germinal identification. In addition to the morphologic and tinctorial methods of older observers, the experimental worker of today bases his conclusions on physiologic criteria. The macrophage or histiocyte possesses the following known physiologic properties: 1. It is essentially phagocytic. 2. It takes up vital dyes in a specific manner storing them in its cytoplasm. 3. It is a "lipoidophage." 4. Under the influence of proper stimuli, it undergoes certain morphologic changes and proliferates "recklessly."

The cells lining the wall of the pulmonary alveoli comply with the enumerated requirements. I believe, therefore, that they are macrophages.

SUMMARY

The loose connective tissue, particularly the mesenchymal cells (macrophages) which it harbors, plays a rôle in immunity, in infection and in the metabolism of different substances, thus representing a defensive and metabolic apparatus of the organism. It is furthermore possible that mesenchymal tissues also possess properties of internal secretion.

The lungs possess a highly developed mesenchymal, that is, a defensive and metabolic, apparatus. Macrophages are present in the wall of the alveoli and also in the peribronchial and the perivascular connective tissue. Pluripotential mesenchymal cells, moreover, line the air spaces themselves.

These alveolar wall cells, in a manner typical of the large mononuclear phagocyte, the macrophage, phagocytose and store dyes and oils, respectively. Stimulated by these substances, they immediately pro-

43. Quoted by Lubarsch, O.: Arb. a. d. Path. Inst., Posen, 1901.

44. S. B. Rose, in a recent publication (The Finer Structure of the Lung, *Arch. Path.* **6**:36 [July] 1928), produced evidence that the lung is developed from two germ layers, endoderm for the bronchi and mesoderm for the capillaries and cuboidal cells. He concluded therefore that the embryologic observations of the lung noted by him favor my conception of the mesenchymal nature of the cells lining the air sacs.

liferate and separate from the alveolar wall, forming the intra-alveolar "inflammatory exudate" (the "dust cells," the "heart failure cells"). Under the influence of the intratracheally injected oil, they form typical giant cells of the Langhans type.

In three examples of human lungs, the cells lining the wall of the alveoli displayed characteristics noted in the lungs of animals during experimental work.

THE REACTION OF THE OLIGODENDROGLIA TO INJURY OF THE BRAIN *

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AND
LEO M. DAVIDOFF, M.D.
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REVIEW OF LITERATURE

The majority of writers have apparently accepted the point of view that the neurologlia cells are of ectodermic origin. Some, however, still believe that they are derived from the mesoderm (Rezza,[1] Pfanner[2]). Various investigators have expressed the opinion that among neuroglia cells of ectodermic origin elements of mesodermic origin are also generally found. The latter view is rather old; according to Del Rio Hortega,[3] it can be traced as far back as 1875, in a work of Eichhorst,[4] who detected in the fourth month of fetal life the presence in the human central nervous system of immigrated white blood cells, which, following their fixation in the nervous tissue, became transformed later into astrocytes. His[5] also reported, in 1890, the presence in the nervous tissue of mesodermic corpuscles, immigrating into the gray and white matter and developing, in a further stage, protoplasmic prolongments. Lachi,[6] Paladino,[7] and Capobianco and Fragnito[8] also reached the conclusion that among ectodermic elements neuroglia cells of mesodermic origin were commonly found. However, while for His the astrocytes (cells of Deiters) are the cells of mesodermic origin, for Fragnito and Capobianco the adendritic cells are the ones which are derived from the mesoderm.

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* From the Neuropathological Department of the New York State Psychiatric Institute.

* Read at the Fifty-Fourth Annual Meeting of the American Neurological Association, Washington, D. C., May 1, 1928.

1. Rezza, A.: Mesenchima (sistema reticolo endoteliale), Riv. Sper. di freniat. **48**:558, 1924.

2. Pfanner, A.: Subependymal Gliosis in a Case of General Paralysis, Arch. gen. di neurol. e psichiat. **8**:1 (April) 1927.

3. Del Rio Hortega, P.: El tercer elemento de los centros nerviosos histogenesis y evolution normal, Arch. de neurobiol. **11**:212, 1921.

4. Eichhorst, H.: Ueber die Entwicklung des menschlichen Rueckenmarks und seiner Formelemente, Virchow's Arch. f. path. Anat., 1875, vol. 64.

5. His, W.: Histogenese und Zusammenhang der Nervenelemente, Arch. f. Anat. u. Entwicklngsgesch., Anat. Sect., 1890, p. 95.

6. Lachi, P.: Contributo alla istogenesi della neuroglia nel midello spinale, Pisa, 1890.

7. Paladino, quoted by Rezza (footnote 1).

8. Capobianco, A., and Fragnito, O.: Nuove cicerche sulla genesi e i rapporti nutritivi degli elementi nervosi e nevroglia, Ann. di nevrol. **16**:81, 1898.

Even in the early nineties, therefore, the conception that some neuroglia cells might be of mesodermic origin was already based on careful embryologic investigations, and Paladino had already applied the term "ectoglia" to the elements derived from the ectoderm and "mesoglia" to the other constituents.

In 1899, Ford-Robertson [9] recalled attention to the subject by describing the presence of prolongments in neuroglia cells considered of mesodermic origin, which he was able to impregnate by a method of his own (platinum mercuric chloride). In a paper read by Dr. Clouston [10] at the fifty-ninth annual meeting of the Medico-Psychological Association, in 1900, it was asserted that:

> Ford-Robertson discovered that in addition to the common type of neuroglia there is another set of cells which he called the "mesoglia" consisting of a typical form of cell body, a nucleus and a number of processes. These processes are in no way connected either with the vascular substance or with the nerve cells or the nerve fibers. The mesoglia cells are entirely different from neuroglia cells in appearance and are found in both the white and gray matter and in such abundance that Dr. Robertson thinks that there are as many mesoglia cells as there are neuroglia cells. Sometimes they have no processes, sometimes two processes. The exact function of these neuroglia cells we certainly do not know but they do not act in any way as a support to the general brain structure. The mesoglia cells seem to have a phagocytic action in certain pathological conditions. They supply if not all at least the greater part of the amyloid bodies which are found in some of the chronic brain degenerations.

In the work of Ford-Robertson mention is not found, of course, of a distinction between the elements now known as oligodendroglia and microglia, although from the drawings appearing in his textbook of morbid pathology we feel safe in assuming that the cells which Robertson succeeded in impregnating were both oligodendroglia and microglia (fig. 1). Indeed, a definite distinction was made only a few years ago through the careful investigations of Del Rio Hortega,[11] who separated these cells into two categories, i.e., the oligodendroglia, or "glia de escasas radiaciones," and the microglia. Both these elements belong to the so-called third element of Cajal,[12] who distinguished in the central

9. Ford-Robertson, W.: A Textbook of Pathology in Relation to Mental Diseases, Edinburgh, W. F. Clay, 1900.

10. Ford-Robertson, W.: A Microscopic Demonstration of the Normal and the Pathological Histology of Mesoglia Cells (read by Dr. Clouston at the Fiftieth Annual Meeting of the Medico-Psychological Association), J. Ment. Sc. **46**:724, 1900.

11. Del Rio Hortega, P.: Estudios sobre la neuroglia; la glia de escasas radiaciones (oligodendroglia), Bol. de la real Soc. Espanola de historia natural. Jan. 10, 1921.

12. Cajal, S. R.: Contribucion al conoscimiento de la neuroglia del cerebro humano, Trab. d. lab. de invest. biol. Univ. de Madrid **11**:254, 1913.

nervous system a first element (nerve cells), a second element (neuroglia cells) and a third element (adendritic bodies) corresponding also to the interstitial corpuscles of Achucarro,[13] and the cells of Robertson and Del Rio Hortega. According to the latter, however, the cells which Robertson denominated "mesoglia" are exclusively represented by oligodendroglia cells, and he is opposed to the characterization by Cajal[14] of "mesoglia of Robertson and Del Rio Hortega" as though "mesoglia" applied to both types of cells, claiming for himself the first description of the microglia.

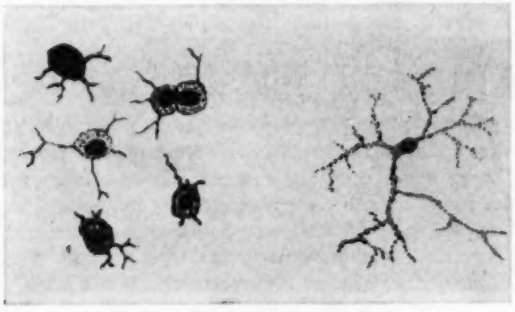

Fig. 1.—Drawings illustrating the "mesoglia." (After Robertson: The Pathology of Mental Disease, Edinburgh, William F. Clay, 1900.)

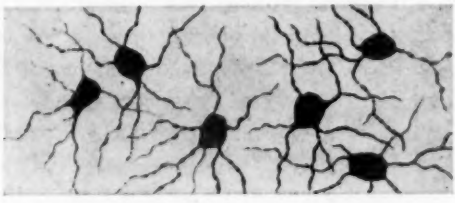

Fig. 2.—Oligodendroglia stained by the method of Robertson (after Del Rio Hortega).

The two types of cells differ from each other not only in point of morphology, but in that of embryology and that of function. In point of morphology, better than any description, the reproduction of two pictures taken from an original work of Del Rio Hortega will give a correct idea of the striking difference between the two (figs. 2 and 3).

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13. Achucarro, N.: Neuroglia y elementos intersticiales patologicos del cerebro impregnados por los metodos de reducion de la plata, Trab. d. lab. de invest. biol. Univ. de Madrid **9**:161, 1911.

14. Cajal, S. R.: Algunas consideraciones sobre la mesoglia de Robertson y Del Rio Hortega, Trab. d. lab. de invest. biol. Univ. de Madrid, 1920, vol. 17.

The shape of the cell; the size and shape of the nucleus, small and triangular in the microglia, large and round in the oligodendroglia; the number of the prolongments; their direction and their ramification establish such differences that further description is not needed. The same morphologic characters are seen whether the cells are free in the tissue or occupy the position of satellites (perineuronal and perivascular) (figs. 1 and 5).

Embryologically, the oligodendroglia are considered by many to be of ectodermic origin. In a detailed work (1921), Hortega,[15] for example, concluded that the oligodendroglia cells arise from the ectoderm (ependyma), while the microglia arise from the mesoderm (meninges, blood vessel walls, and superior and inferior tela corodea). The microglia, which are then migratory cells, owe their typical appear-

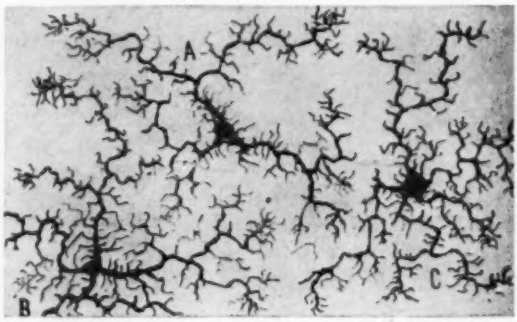

Fig. 3.—Microglia cells: (*A*) tripolar; (*B*) tetrapolar and (*C*) multipolar (after Del Rio Hortega).

ance to their adaptation to the interstitial spaces of the central nervous tissue.

The function of the microglia cells is said also to differ entirely from the function of astrocytes and oligodendroglia cells. While the astrocytes are related to the process of repair, the microglia develop a decided phagocytic function, which is believed never to be performed by any of the other interstitial elements of the central nervous system. This fact was considered by Del Rio Hortega as a valid argument in support of his conception of the mesodermic origin of microglia. In a further development of this conception, Jiminez de Asua,[16] a pupil of Del Rio Hortega,

15. Del Rio Hortega, P.: La microglia y su transformation en celulas en bastoncito y cuerpos granulo adiposos, Trab. d. lab. de invest. biol. Univ. de Madrid, 1920, vol. 18.

16. Jimenez de Asua, T.: Die Mikroglia (Hortegazellen) und das reticuloendotheliale System, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:354, 1927.

succeeded in impregnating with silver carbonate, in different organs of the body, mainly the spleen, and in pathologic tissues, namely, granulomas or tumors, macrophages of mesodermic origin which morphologically look like the microglia of the central nervous system, especially during their stage of transformation into scavenger cells. Because of morphologic, chemical, embryologic, and functional resemblances between these phagocytes and the microglia, De Asua expressed the belief that the latter probably belong to the same reticulo-endothelial system from which phagocytes originate.

However, the proof for the mesodermic origin of the microglia does not go entirely unchallenged. Among others, Metz and Spatz [17] have

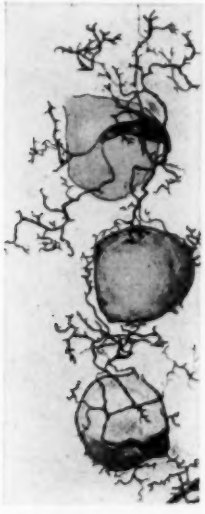

Figure 4

Figure 5

Fig. 4.—Microglia satellites about neurons from the cerebral cortex (after Penfield).

Fig. 5.—Oligodendroglia satellites about neurons from the cerebral cortex (after Penfield).

recently objected to this conception. Nor does the belief in the origin of scavenger cells exclusively from microglia, win unanimous accord. Several writers are still of the opinion that the aforementioned cells may be derived from astrocytes. As a matter of fact, the question of origin of the compound granular corpuscles has always been a point of

17. Metz, A., and Spatz, H.: Die Hortegaschen Zellen (das sogenannte dritte Element) und ihre funktionelle Bedeutung, Ztschr. f. d. ges. Neurol. u. Psychiat. **89**:138, 1924.

difference among investigators. Nissl,[18] Stroebe,[19] Farrar,[20] Cajal, Ribbert,[21] Bonome, Devaux,[22] Righetti, Guizetti,[23] O. Rossi [24] and Ziveri [25] held to a mesodermic origin; Marchand,[26] Friedman,[27] Bonfiglio,[28] Merzbacher,[29] L'hermitte and Schaeffer,[30] Schilder,[31] Pandolfi [32] and Jakob [33] believed in a combined mesodermic and ectodermic origin, and Schmaus,[34] Schroeder,[35] Lotmar [36] and Anton and Wohl-

18. Nissl, F.: Ueber einige Beziehungen zwischen Nervenzellerkrankungen und gliosen Erscheinungen bei verschiedenen Psychosen, Arch. f. Psychiat. **32**: 656, 1899; Zur Histopathologie der paralytischen Rindenerkrankung, in Nissl-Alzheimer: Patholischen Arbeiten, 1904, vol. 1.

19. Stroebe, H.: Ueber Struktur pathologischer Neurogliawucherung, 68, Verhandl. d. Gesellsch. deutsch. Naturf. u. Aerzte zu Frankfurt, 1896.

20. Farrar, C. B.: The Phenomena of Repair in the Cerebral Cortex, etc., Histol. u. histopath. Arb. ü. die Grosshirnrinde, Jena **3**:1, 1908.

21. Ribbert, quoted by Ziveri (footnote 26).

22. Devaux: Etude histologique des foyers de nécrose de l'écorce cérébrale, Histol. u. histopath, Arb. ü. die Grosshirnrinde **2**:115, 1908.

23. Guizzetti: The Pathology of the Nervous System, in Foa: Textbook of Pathologic Anatomy, Societa Editrice tipografico Torinese, 1922.

24. Rossi, O.: Processi rigenerative e degenerativi conseguentia ferite asettiche del sistema nervoso centrale, Riv. di patol. nerv. **13**:481, 1908.

25. Ziveri, A.: Alcune considerazioni sulla cosidetta neuroglia adendritica ("tercer elemento" di Cajal), Ann. di nevrol. **32**:235, 1914.

26. Marchand, F.: Herkunft der Kornchenzellen des Zentralnervensystems, Beitr. z. path. Anat. u. z. allg. Pathol. **45**:161, 1909.

27. Friedman: Chapter on Nonsuppurative Encephalitis in Flatau-Jacobson: Textbook of Morbid Pathology of the Nervous System, Societa Editrice Torinese, Turin, 1909.

28. Bonfiglio, F.: Circa le alterazioni della corteccia cerebrale conseguenti ad intossicazione sperimentale da carbonato di piombo, Histol. u. histopath. Arb. ü. die Grosshirnrinde **3**:359, 1909.

29. Merzbacher, L.: Untersuchungen ueber die Morphologie und Biologie der Abraumzellen im Zentralnervensystem, Histol. u. histopath. Arb. ü. die Grosshirnrinde **3**:1, 1909.

30. L'hermitte, J., and Schaeffer, H.: Les phénomènes réactionels du ramollissement cérébral aseptique, etc., Semaine méd. **33**:25, 1910.

31. Schilder, P.: Zur Frage der Encephalitis periaxialis diffusa (sogenannte diffuse Sklerose), Ztschr. f. d. ges. Neurol. u. Psychiat. **15**:359, 1913.

32. Pandolfi, G.: La nevroglia nelle intossizioni, Ann. di nevrol. **31**:161, 1913.

33. Jakob, A.: Ueber die feinere Histologie der sekundaeren Faserdegeneration in der weissen Substanz des Rueckenmarks, Histol. u. histopath. Arb. ü. die Grosshirnrinde, 1914, vol. 5.

34. Schmaus, H.: Vorlesungen über die pathologische Anatomie des Rueckenmarks, Wiesbaden, J. Bergmann, 1901, vol. 21; quoted by Bolsi: Riv. di patol. nerv. **32**:907, 1928.

35. Schroeder, quoted by Bolsi: Riv. di patol. nerv. **32**:907, 1928.

36. Lotmar, F.: Beiträge zur Histologie der akuten Myelitis und Encephalitis, sowie verwandter Prozesse, Histol. u. histopath. Arb. ü. die Grosshirnrinde **1**:245, 1913.

will [37] upheld an exclusively ectodermic origin. Recently Spatz, Metz and Creutzfeldt [38] returned to the subject, claiming that scavenger cells arise from both microglia and astrocytes. These writers go a point beyond the old conception of Alzheimer,[39] however, for whom the scavenger function was common to all types of glia cells. According to them, a distinction has to be made between the mobile and fixed type of scavenger cells. While the mobile scavenger cells, they claim, result from the transformation of microglia elements, the fixed scavenger cells are derived from transformed astrocytes.

With authorities thus about equally divided, we felt that the field was open to further investigation, especially regarding the question of origin of the compound granular corpuscles. Since various workers had already confirmed Hortega's conclusion as to the transforma ion of microglia into these elements, we decided to concentrate our attention on the general reaction of the second constituent of the third element following brain injuries and its possible participation in the formation of scavenger cells. For, with regard to the relation of the oligodendroglia to formation of compound granular corpuscles, we have not been able to find anything in the literature more definite than a mention in Timmer and Prijus' work that oligodendroglia cells may be transformed into compound granular corpuscles. Indeed, altogether, little has been published dealing with the oligodendroglia cells, other than Hortega's papers and the ones of Penfield and Cone,[40] Bailey and Schaltenbrandt,[41] Urecchia and Elekes.[42] Only occasional mention of oligodendroglia is found in the work of Baumann, Timmer,[43] Bolsi,[44] Winkler [45] and Pruijs.[46]

37. Anton, G., and Wohlwill, F.: Multiple nicht eitrige Encephalomyelitis, Ztschr. f. d. ges. Neurol. u. Psychiat. **12**:31, 1912.

38. Creutzfeldt, H. G., and Metz, H.: Ueber Gestalt und Taetigkeit der Hortegazellen bei pathologischen Vorgaengen, Ztschr. f. d. ges. Neurol. u. Psychiat. **106**:18, 1926.

39. Alzheimer, A.: Beiträge zur Kenntnis der pathologischen Neuroglia, Histol. u. histopath. Arb. ü. die Grosshirnrinde, 1921, vol. 3.

40. Penfield, W., and Cone, S.: Acute Swelling of Oligodendroglia; Specific Type of Neuroglia Change, Arch. Neurol. & Psychiat. **16**:13 (Aug.) 1926.

41. Bailey, P., and Schaltenbrandt, G.: Die mukoese Degeneration der Oligodendroglia, Deutsche Ztschr. f. Nervenh. **97**:230, 1927.

42. Urecchia, C., and Elekes, N.: Contribution à l'étude des plaques séniles, etc., Bull. Acad. de méd., Paris **18**:795, 1925.

43. Timmer, quoted by Winkler: Psychiat. Neurol., 1926, p. 101.

44. Bolsi, D.: Le transformasioni patologiche della microglia, Riv. di patol. nerv. **32**:907, 1928.

45. Winkler, Junius E.: Die Bedeutung Del Rio Hortega's Neuroglia-Untersuchungen ueber die Histopathologie des Zentralnervensystems Pschiat. en Neurol. Bl., 1926, p. 91.

46. Pruijs, W. M.: Ueber Mikroglia, ihre Herkunft, Funktion und ihr Verhaeltniss zur anderen Gliaelementen, Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:298, 1927.

The first mention of pathologic changes of oligodendroglia, however, can be traced as far back as 1900 to Robertson's textbook, in which the author states that these cells undergo phagocytic changes. In 1925, the interesting paper of Penfield and Cone was published dealing with another pathologic change of this element; that is, the so-called acute swelling of the oligodendroglia. This lesion consists of a gradual swelling of the cytoplasm of the cell, which at its height may be followed by the breaking up of the cell and its disintegration. In 1927, Bailey and Schaltenbrandt detected the presence of mucine in the swollen oligodendroglia cells. It must be pointed out, however, that Pelissier,[47] a pupil of Grynfeltt,[48] was the first to suggest that the mucocytic degeneration of the neuroglia is the result of mucine degeneration of oligodendroglia cells. Another work dealing with the pathology of oligodendroglia is the one of Urecchia and Elekes, who consider the senile plaque to be the result of the primary degeneration of oligodendroglia elements.

PRESENT INVESTIGATION

Our experiments consisted of the histologic examination of the brains of twenty-two cats at varying intervals (twelve hours to two months) following the aseptic removal of a portion of cerebral hemisphere. After the animal was killed, the region of the lesion was immediately fixed in a solution of formaldehyde-bromide, and the method specific for the staining of the oligodendroglia was applied. (In this connection we wish to express our thanks to Dr. Penfield and Dr. Cone for their valuable suggestions.) We obtained very good results by fixing fresh material for only four hours in formaldehyde-bromide and then treating the sections by the original Hortega method. Constant results were also obtained by the use of the combined method for staining oligodendroglia and microglia, as reported by Penfield in the March, 1928, issue of the *American Journal of Pathology*.

Acute Swelling of the Oligodendroglia.—In the early stages (twelve hours) following the injury to the brain, the first reaction of the oligodendroglia appears to be in the cortex immediately surrounding the lesion. There the cells disclose all the typical changes described by Penfield and Cone as the acute swelling of the oligodendroglia (fig. 6). The earliest change seems to be an irregular condensation of the perinuclear cytoplasm and then swelling of the cell body. Unstainable fluid

47. Pelissier, G.: Syndrome Wilsonien consécutife a la névraxite èpidemique—contribution a l'étude de la degenerescence mucocytaine de la nevroglie, Thèse de Montpellier, 1924.

48. Grynfeltt, E.: Mucocytes et leur signification dans les processes de l'inflammation chronique des centres cérébraux-spinaux, Compt. rend Soc. de biol, 1923. vol. 89.

pushes out the cell membrane and granules are seen on the surface of the membrane and around the septums or protoplasmic girders which separate the vacuoles within the cell body. The protoplasmic expansions then decrease in number and are represented by chains of granules. In some cases the nucleus is extruded out of the cell body leaving an empty shell behind, while in others the cell membrane ruptures, the cytoplasm disintegrates and the nucleus appears naked in the tissue. The nuclei themselves vary in the different stages, staining with a greater or less intensity, appearing at times somewhat swollen and at others progressively shrunken and pyknotic (fig. 7).

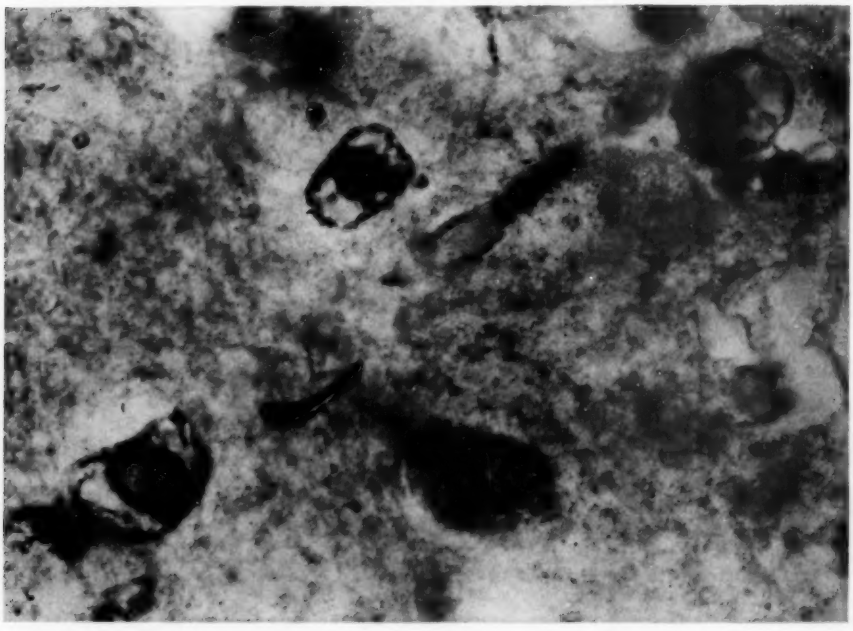

Fig. 6.—Photomicrograph of acute swelling in an oligodendroglia cell; stained by the silver carbonate method; × 1000.

The acute swelling is still encountered after twenty and after forty-eight hours. Following this period, acute swelling is seldom met with; thus it is an early and transitory reaction of the oligodendroglia. The acute swelling, in fact, may be a reversible phenomenon, as held by Penfield and Cone, and we are inclined to think that the absence of acute swelling in more advanced stages of injury to the brain may be the result of such reversibility. Not all the swollen cells, however, revert to their original state. Some of them disintegrate and disappear, while others, as we will set forth later, are transformed into scavenger cells.

It may be of interest to note that the swelling of the oligodendroglia occurs less markedly and less uniformly in the white substance immediately surrounding the lesion than in the gray matter, where this type of reaction occurs regularly and intensely.

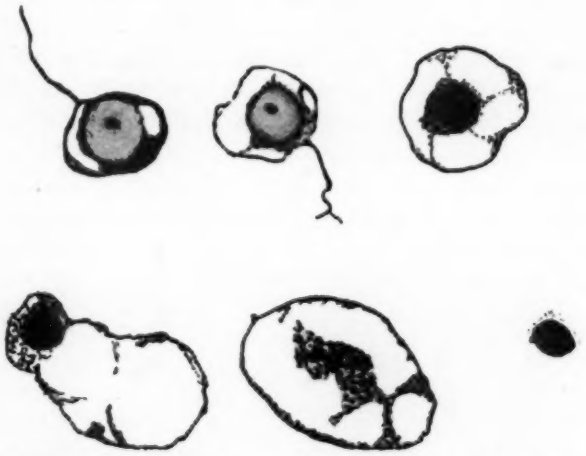

Fig. 7.—Drawing showing various stages of acute swelling of oligodendroglia cells; stained by the silver carbonate method.

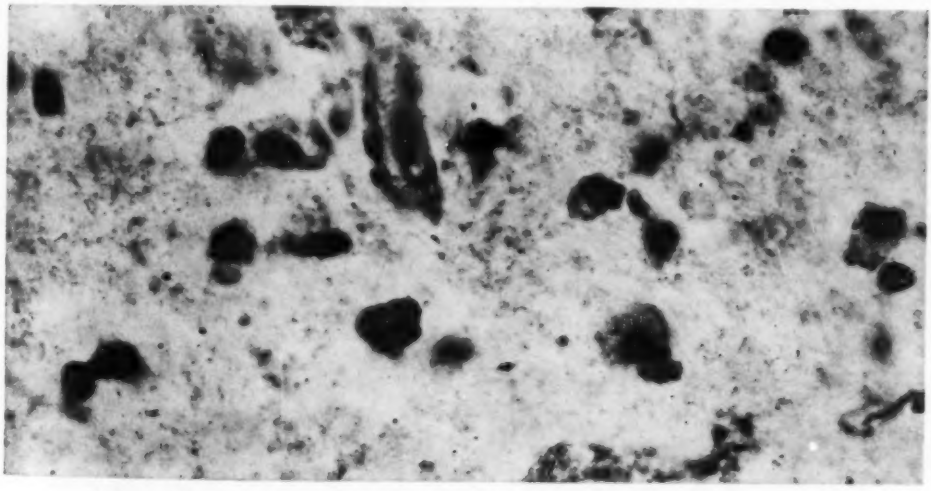

Fig. 8.—Photomicrograph showing atrophic degeneration of oligodendroglia; stained by the silver carbonate method; × 1000.

Atrophic Degeneration of the Oligodendroglia.—Besides the acute swelling, in the early stages of reaction, another important change is found which involves the central area of the lesion and which we consider the expression of an atrophic degenerative change of the oligoden-

droglia cells. In this case the whole cell appears shrunken, with a retracted cytoplasm and irregular outlines. The shrinkage of the cytoplasm is at times concentric, leading to the formation of small elements in each of which the nucleus is surrounded by a small ring of protoplasm. The nucleus undergoes definite changes, the most important of which is hyperchromatosis. The deeply impregnated appearance may affect a nucleus which still maintains its round shape. In a more advanced stage of the atrophic process, the nucleus undergoes a process of pyknosis; that is, deformation and granular disintegration, leading to the disappearance of the element (fig. 8).

An ultimate stage of atrophy may be the asteroid aspect of the cell, in which the nucleus appears deeply stained and with radiary small pro-

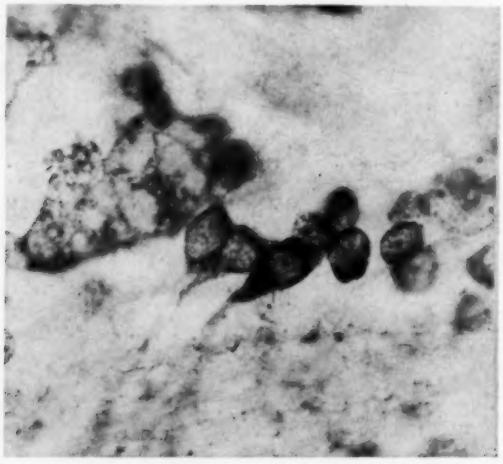

Fig. 9.—Photomicrograph showing normal oligodendroglia; stained by the silver carbonate method; × 1000.

longments, the residuum of the disintegrated cytoplasm. Such a stage has been described by Urechia and Elekes in their study on the senile plaques. As in the case with the neuroglia cells, the atrophy may be secondary, involving a cell which is already undergoing some other pathologic change, as for instance, swelling or hypertrophy.

Atrophic changes of the oligodendroglia cells are encountered in various stages following brain injury. They may be found as soon as twelve hours afterward, and are still present in cases of two and four weeks' standing. The atrophic cells usually occupy the central area of the lesion, where the necrotic process is at its height. Atrophic cells are seldom encountered in areas distant from the lesion.

Hypertrophy of the Oligodendroglia.—In contrast to the atrophic changes of oligodendroglia are the hypertrophic changes, which appear

extremely important to us. The hypertrophy of the element consists in a true growth of the cell body, which discloses an increased cytoplasm, and active nucleus and enlarged prolongments. The degree of hypertrophy varies according to the stage of the lesion. It is not present in the early stages; twenty hours following the operation, definite hypertrophic changes are seen in the elements immediately surrounding the lesion. The hypertrophy seems to affect mainly the cells lying in the white substance. In the gray matter only occasional enlarged cells are detectable. The hypertrophic changes appear to grow more pronounced as the age of the lesion advances, reaching their maximum three or four days following the injury. In figure 9, where oligodendroglia cells of normal appearance are reproduced, it may be observed that the cytoplasm surrounding the nucleus is small in amount and has a tendency to occupy

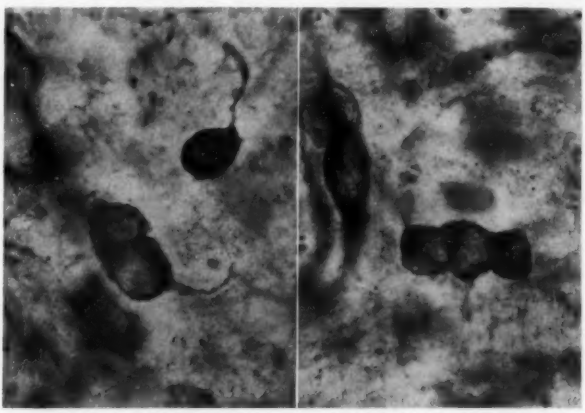

Fig. 10.—Photomicrograph indicating the collection in clusters of two and three oligodendroglia elements; stained by the silver carbonate method; × 1000.

one of the poles of the cell body, thus giving to the element a piriform shape. Although a difficult task, we have nevertheless succeeded in reproducing in our photomicrographs some of the prolongments of both normal and hypertrophic cells. The normal elements, as shown by Robertson's first drawing, possess a few prolongments which may show intercalated swellings. The cells, which are found in both the gray and the white substance, contribute to the formation of the so-called satellite cell of both the nerve cells and the blood vessels. The morphologic differences between satellites of oligodendroglia and microglia origin are quite definite, and the comparison of figures 4 and 5, in which they are reproduced, gives a better idea than any detailed description. The existence of sucker feet in oligodendroglia has been denied by Robertson and Hortega. In this connection, however, we may say that in many instances we were able to follow prolongments of the oligodendroglia

cells which reached the blood vessel walls, where they apparently ended. Although it may be possible that some of the prolongments simply crossed the blood vessel, in a few instances our impression was definite as to the arrest of the prolongment along the blood vessel wall, where, occasionally, it even ended with a kind of thickening recalling the aforementioned sucker foot. Indeed, Bailey and Schaltenbrandt, in their valuable study of the perivascular spaces, mentioned the fact that oligodendroglia cells with their blood vessel attachment contribute to the formation of the pia-glial membrane. This particular point deserves further investigation, as its confirmation would establish more analogies between astrocytes and oligodendroglia cells.

Another point which is brought out from our study of the oligodendroglia is their tendency to collect in clusters of two or more cells (fig. 10). This tendency may lead to the fusion of the elements into a symplasma formation (fig. 11) in which two or more nuclei are found.

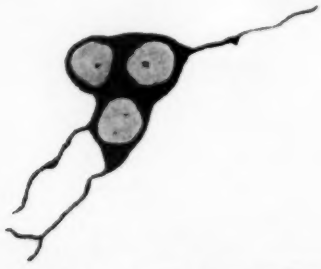

Fig. 11.—Drawing to show the fusion of three oligodendroglia cells (as stained by the silver carbonate method).

For the appearance of the hypertrophic changes we are submitting figure 12, in which a certain amount of hypertrophy of the cell body is noticeable as compared with the normal elements seen on the left side of the picture. In a more advanced stage (fig. 13) the hypertrophy is somewhat more marked, and two hypertrophic cells are reproduced, the upper one of which has no definite prolongments while the lower one shows a strongly developed and dichotomized prolongation. In the drawing represented in figure 14, a more pronounced hypertrophy is registered, the cytoplasm having increased to more than twice the size of the nucleus, while the prolongments may be followed for a considerable distance. Well outlined prolongments may also be seen in figure 15. Finally, in a still more advanced stage, the hypertrophic elements appear as huge cells in which the cytoplasm is markedly increased and the prolongments are definitely enlarged (fig. 16). In advanced stages the nucleus also participates in the hypertrophic process. This structure in conditions of true hypertrophy of the cell keeps its active normal char-

acters, contrasting with its shrunken and pyknotic aspect in conditions of pseudohypertrophy as represented, for instance, by the acute swelling of the oligodendroglia.

Hyperplasia of the Oligodendroglia.—Besides the hypertrophy of the single elements, a true hyperplasia occurs. It is not easy to deter-

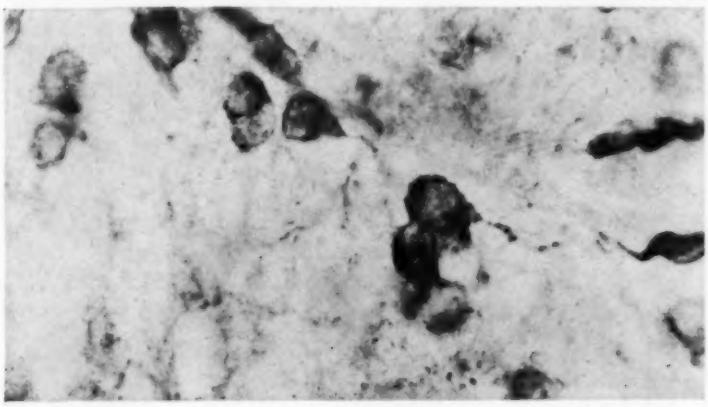

Fig. 12.—Photomicrograph of an early stage of hypertrophy of an oligodendroglia cell; stained by the silver carbonate method; × 1000.

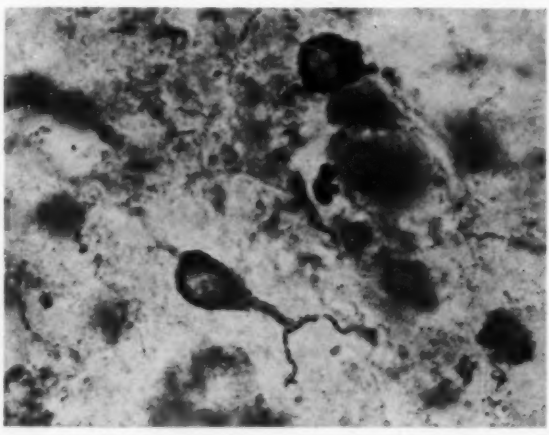

Fig. 13.—Two hypertrophic oligodendroglia cells, one of which shows hypertrophy of its prolongations; stained by the silver carbonate method; × 1000.

mine whether the proliferation of oligodendroglia cells takes place through a process of mitosis alone or by means of both mitotic and amitotic division. As is the case with the neuroglia cells, a mitotic process may be detected occasionally, as in the cell shown in figure 17. The cell undergoing mitosis seems to us to belong to the oligodendroglia

group because of its peculiar location and orientation. At any rate, surrounding the area of necrosis, places are seen in which oligodendroglia cells, more numerous than in normal conditions, are collected. Numerous elements are also seen surrounding some of the blood vessels, around which they collect as isolated cells or as clusters.

Formation of Compound Granular Corpuscles.—The demonstration of the transformation of the oligodendroglia cells into scavenger cells

Fig. 14.—Drawing to illustrate advanced hypertrophy of an oligodendroglia cell with well outlined prolongments (as stained by the silver carbonate method).

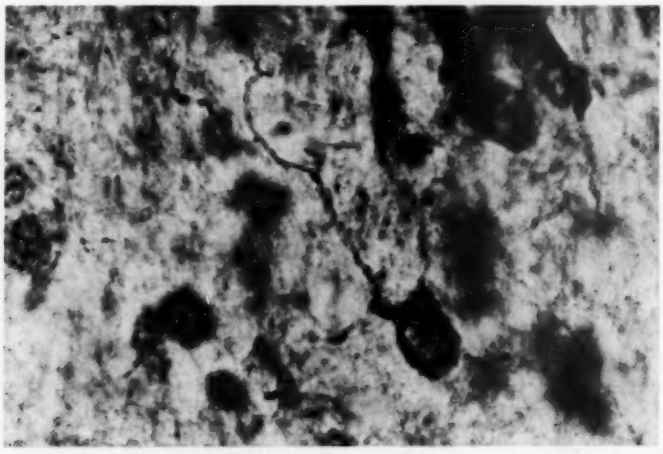

Fig. 15.—Photomicrograph showing the hypertrophy and elongation of the prolongments; stained by the silver carbonate method; × 1000.

seems to us to be the most important point of our investigation. In our series of cases, we have indeed been able to follow all the transitory stages of transformation between oligodendroglia cells and compound granular corpuscles. This particular point has never before been thoroughly investigated; only occasional remarks are found in the literature as to the possible transformation of the oligodendroglia into scavenger

cells. It may, however, be recalled that already Robertson had claimed that his mesoglia cells contribute to the formation of the compound granular corpuscles. If we were to believe with Del Rio Hortega that

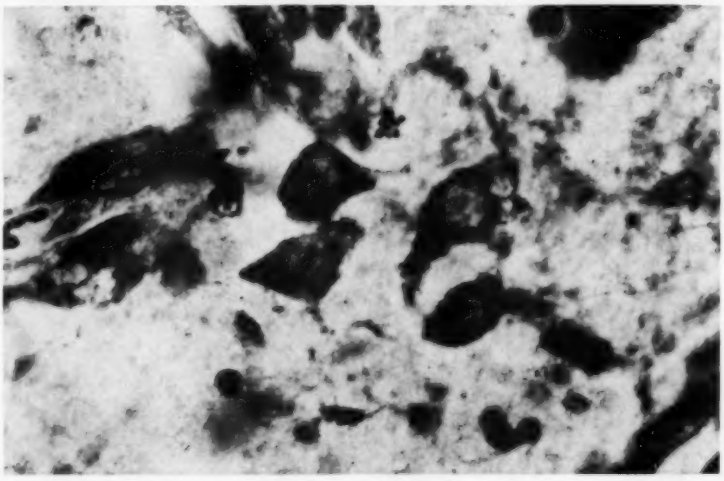

Fig. 16.—Final stage of oligodendroglia hypertrophy, showing marked increase in cytoplasm and thickness of its prolongments; stained by the silver carbonate method; × 1000.

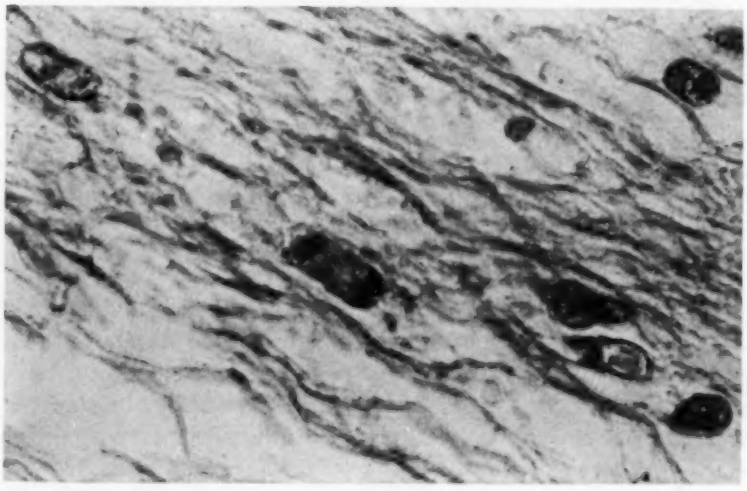

Fig. 17.—Oligodendroglia cell undergoing mitosis; stained with Meyer's mucicarmine stain and counterstained with methyl violet; × 1000.

Robertson saw only oligodendroglia cells in his preparations, we should thus have a confirmation of our contention by that astute observer. Since, however, in the pictures related to his work, cells are also shown

morphologically like microglia, the doubt is justifiable as to which of the two elements he saw transforming into the compound corpuscles.

In our material we have been fortunate enough to follow their definite transition, so that we feel justified in making the statement that compound granular corpuscles arise from the oligodendroglia, as well as the microglia cells. Indeed, as soon as twelve hours after the injury to the brain, a few oligodendroglia cells are already seen transforming into compound granular corpuscles. The fact is more evident in twenty hours and becomes definite forty-eight hours after the injury. From that time on, the transformation continues and may still be detectable in two months old material.

According to our investigations, the compound granular corpuscle may arise from three types of oligodendroglia cells: (*a*) normal oligo-

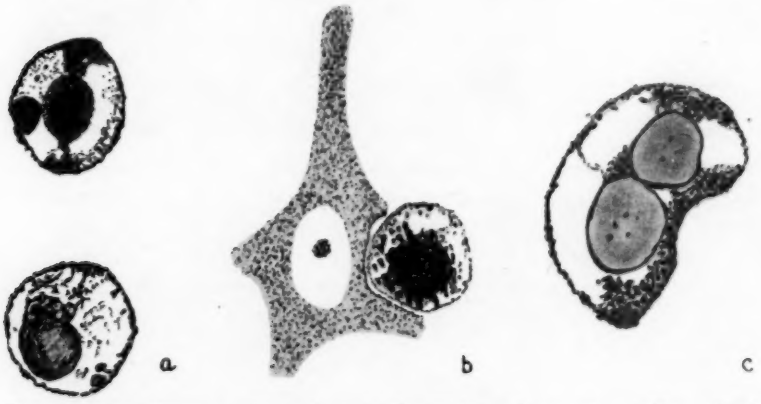

Fig. 18.—Drawings to show the transformation of acutely swollen oligodendroglia into compound granular corpuscles; stained by combined silver carbonate and Fettpenceau; *a* shows appearance of a few fat granules in the swollen cytoplasm of the cell; *b*, a satellite cell, and *c*, oligodendroglia cell which has fused into larger unit.

dendroglia cells, (*b*) hypertrophic oligodendroglia cells and (*c*) acutely swollen oligodendroglia cells. The transformation of a swollen oligodendroglia cell into a compound granular corpuscle may be followed in stages if the proper counterstain is made. We made our preparations by counterstaining our sections treated by the silver carbonate method with "Fettpenceau," then mounting them in glycerin. The process originates (as may be seen in fig. 18a) in the appearance of a few fat granules in the swollen cytoplasm of the cell. The fat granules gradually increase in number and size and tend to fill the whole structure until the cell acquires the typical morphologic aspect of a compound granular corpuscle. The transformation affects both the isolated and the satellite elements. In figure 18b a satellite cell is drawn, and its morphology

leaves no doubt as to its oligodendroglial nature. One should remember here that the microglia cells may also undergo a process of swelling, following which the prolongments are fragmented. The confusion, however, with a swollen cell of microglial origin is easily avoided by attention to the morphologic appearance of the cell body and of the nucleus, so different in the two types of cell. The fact, however, that microglia cells do at times pass through a stage of swelling before their transformation into compound granular corpuscles, seems to us an important one, as it establishes an analogy between the processes of transformation in the two elements. The presence of fat in swollen cells is not only detected in isolated elements, but is seen also in oligodendroglia cells which have fused into a larger unit (fig. 18c). Thus

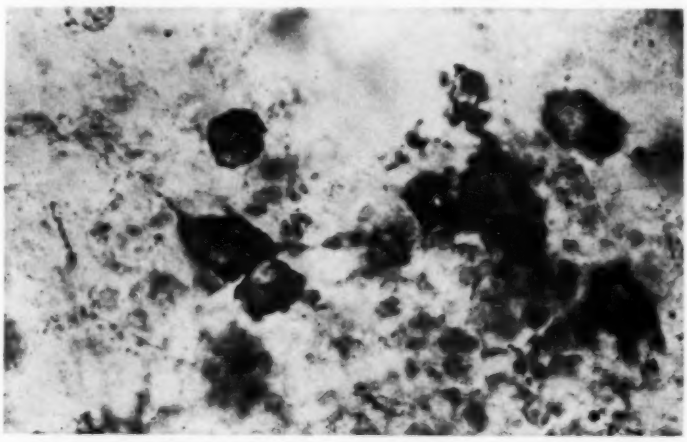

Fig. 19.—Oligodendroglia cell showing beginning vacuolization of the cytoplasm; stained by the silver carbonate method; × 1000.

the acute swelling of the oligodendroglia, which may be a reversible process, may also lead, in addition to a primary disintegration, to the formation of compound granular corpuscles.

It seems to us as if the acute swelling and the transformation into scavenger cells are two distinct processes, depending on the severity of the lesion. If the lesion is a mild one and consists of a simple disruption of the osmotic or colloidal equilibrium between the cell body and its surroundings, substances from the nervous tissue, mainly its water component, penetrate into the cell, leading to a swelling which may subside or lead, at times, to the death of the element. If the lesion is somewhat more severe, the protein material may also be imbibed into the cell body, and the mucine product of disintegration may thus be detected. Finally, if the lesion involving the nervous tissue is even more severe, leading

to the disintegration of the elements of the myelin sheaths and of the interstitial tissue, the fat products of disintegration may become located in the oligodendroglia cells, among others, which thus undergo a gradual transformation into compound granular corpuscles.

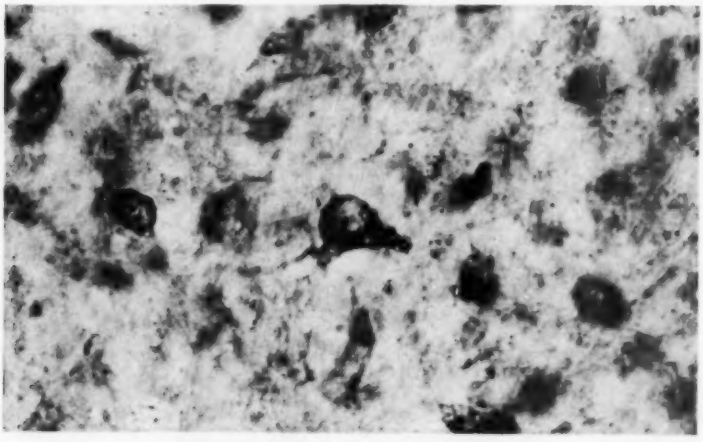

Fig. 20.—A somewhat more advanced stage than that shown in figure 19.

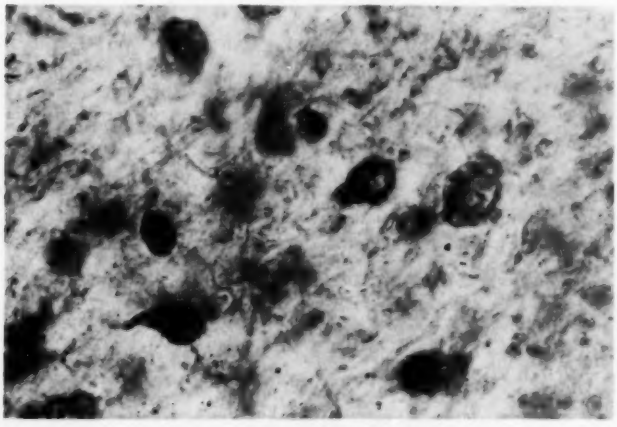

Fig. 21.—The same as figures 19 and 20, showing still more advanced stage, with numerous vacuoles surrounding the nucleus.

The transformation into scavenger cells does not necessarily include a previous stage of acute swelling as such; the change may occur as a direct transformation of normal elements or even of elements which had already undergone hypertrophic changes. In figures 19 and 20, oligodendroglia cells are seen in which several small vacuoles are present in the cytoplasm, mostly on one side of the cell body. In a further

stage, the vacuoles become more numerous in the cytoplasm and tend to surround the nucleus (fig. 21). The presence of vacuoles may not substantially modify the morphology of the original element, which often is well recognizable. In a more advanced stage, the vacuoles

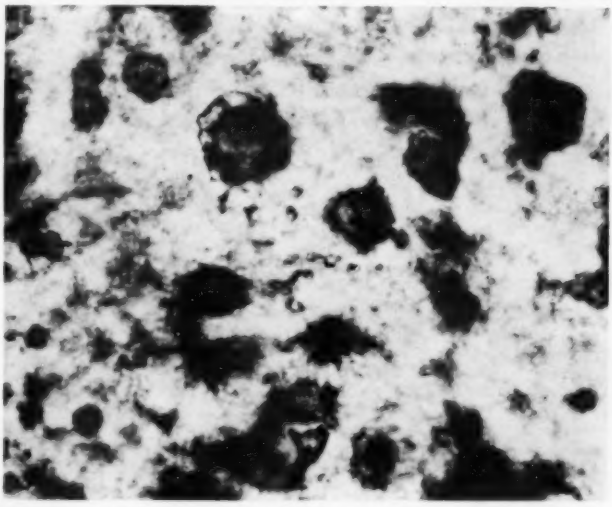

Fig. 22.—Enlarged oligodendroglia with several large vacuoles; stained by the silver carbonate method; × 1000.

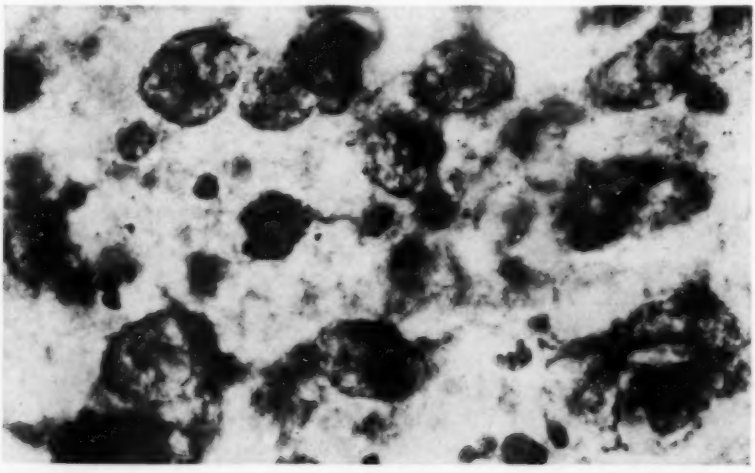

Fig. 23.—Final stage of transformation of oligodendroglia into compound granular corpuscles; stained by the silver carbonate method; × 1000.

increase in size (fig. 22) and number and may lead to an increase in size of the whole cell. In a final stage, the entire cell is filled with vacuoles, which occasionally push aside the nucleus, which may be seen

undergoing a gradual disintegration (fig. 23). All the vacuoles which with the specific stain appear as clear spaces, stain positively with the fat stain.

While undergoing the process of transformation, the oligodendroglia element can for a long time be differentiated from microglia cells undergoing the same transformation. The differentiation can always be made on the basis of an accurate study of the shape of the cell body and of the shape and appearance of the nucleus and the presence of the charac-

Fig. 24.—Drawing showing the various stages of compound granular corpuscles; showing the formation of compound granular corpuscles from normal oligodendroglia cells; stained by the silver carbonate method.

teristic prolongments of the microglia and oligodendroglia cells. The former possess a triangular nucleus, which is strikingly different from the ordinarily round-shaped nucleus of the oligodendroglia cells. It is only in the final stage, when a full blown compound granular corpuscle is formed, that differentiation is difficult and even impossible. In figures 24 and 25, diagrams are reproduced showing the various aspects of oligodendroglia cells undergoing this transformation into compound granular corpuscles.

Not only normal cells, but cells which have already undergone an initial process of hypertrophy may become transformed into compound granular corpuscles. In figure 22, hypertrophic elements are shown, in which an early stage of vacuolization may be detected.

Compound granular corpuscles may also originate from the fusion of two or more oligodendroglia cells. The tendency of these elements to collect into clusters is also detectable in pathologic conditions. As is the case with acute swelling, in which two or more elements are seen fusing together, fused cells may undergo the process of transformation into compound granular corpuscles. Figure 26 reproduces a fusion of several cells showing vacuole formation in the cytoplasm, and figure 27, a

Fig. 25.—Similar to figure 24, but showing the fat granules stained with "Fettpenceau." Combined silver carbonate and Fettpenceau stains were used.

more advanced stage of a similar fusion, the vacuoles of which are even greater in proportion, and are crowding the nuclei aside.

COMMENTS

We have been able to follow in our experiments all the transitory stages between oligodendroglia cells and compound granular corpuscles. We have no doubt as to the validity of our observations, since we have successfully applied the specific method for oligodendroglia evolved by Dr. Penfield out of Hortega's original method, and were able to counterstain these preparations for fat.

The fact that oligodendroglia cells may be seen to transform themselves into compound granular corpuscles weakens the contention of Del

Rio Hortega as to the specific function of the microglia elements. The phagocytic function of the latter as a support for their mesodermic origin cannot now be sustained, since elements of ectodermic origin participate in the same process.

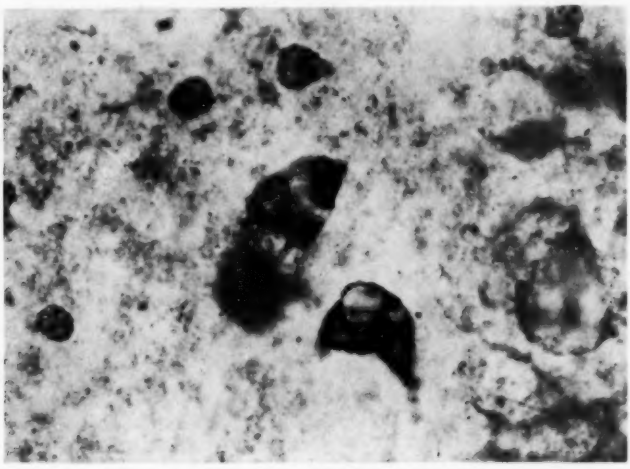

Fig. 26.—A fusion of several oligodendroglia with vacuole formation in the cytoplasm. The silver carbonate method was used; × 1000.

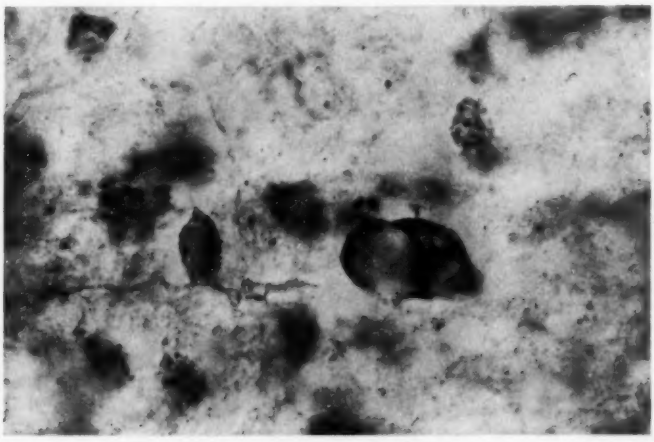

Fig. 27.—Similar to figure 26, but showing a more advanced stage.

If both the constituents of the third element of Cajal (oligodendroglia and microglia) were of common origin, their functional significance would be easier to understand. But as the facts appear to us, the duplex origin of elements the function of which is apparently similar opens the

field to new speculation. On the other hand, the solution of the problem by advocating mesodermic origin for both oligodendroglia and microglia, on the basis only of the similarity of function, would again complicate the situation from the morphologic point of view. For example, transitory forms have been described by Hortega himself between oligodendroglia cells and astrocytes, and the second element of Cajal would thus be dragged into the mêllée.

Further embryologic investigations seem necessary in order to elucidate the origin of both oligodendroglia and microglia, and further experimental studies must be carried on in order to solve the still debated question of the participation of the astrocytes, also, in the formation of compound granule corpuscles. The finding of a common origin for both astrocytes and cells of the third element, whether ectodermic or mesodermic, would probably do most to harmonize the apparently conflicting results of many investigations.

SUMMARY

Experiments were performed consisting in the aseptic removal of a portion of the cerebral cortex in twenty-two cats. At intervals, varying between twelve hours and sixty days after operation, the animals were killed, the brains removed, and the region of the lesion fixed immediately in Cajal's solution of formaldehyde-ammonium bromide mixture. Frozen sections were stained for oligodendroglia and microglia by the silver carbonate technic evolved from Hortega's original method by the modifications introduced by Globus [49] and Penfield. Some of these sections were counterstained, following the silver impregnation, with "Fettpenceau."

The sections thus prepared were examined with a view toward understanding the rôle played by the oligodendroglia in the general reaction to the brain injury. Special attention was paid to the question whether or not these cells participated in the formation of scavenger cells, and to the manner of this participation, if it existed.

CONCLUSIONS

The oligodendroglia cells were found to react to cerebral injury by acute swelling, atrophic degeneration, hypertrophy, hyperplasia, and occasionally by the fusion of several cells into clusters.

It was possible also to demonstrate the transformation of oligodendroglia cells into compound granular corpuscles, and to follow the various stages in this transformation. The change may occur directly from a normal cell or through an intermediary stage of swelling or hypertrophy.

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49. Globus, J. H.: The Cajal and Hortega Glia Staining Methods. A New Step in the Preparation of Formaldehyde-Fixed Material, Arch. Neurol. & Psychiat. **18**:263 (Aug.) 1927.

THE CHEMICAL ANALYSIS OF LIVER AND SPLEEN FROM A CASE OF LIPOID HISTIOCYTOSIS (NIEMANN-PICK'S DISEASE) *

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The purpose of this paper is to report the chemical analysis of the liver and the spleen from a case of lipoid histiocytosis recently recorded by S. L. Berman.[1]

All materials were obtained in the fresh condition. An analysis of the blood for lipoids was made five days before death. A splenectomy was made twenty hours before death. The liver was obtained at necropsy.

Other workers dried their specimens and made ether and alcoholic extracts. Not only is this a long procedure, but it is doubtful if all of the lipoids are extracted. In view of these facts, I extracted the lipoids from the fresh material according to the method of Zelinsky and Zinzadze.[2]

METHOD

Fresh tissue, ground and well mixed, was weighed into a thin-walled pyrex test tube, 2 per cent hydrochloric acid was added, and the tube was sealed. The tissue was then hydrolyzed for two hours at 180 C. (10 atmospheres) in an autoclave. At the end of this period, all the fats and fatty acids floated on the surface of the hydrolysate. The mixture was transferred to a special extractor and extracted with petroleum ether (50 to 60 degrees) for two hours. The extract was dried in a partial vacuum and in an atmosphere of carbon dioxide, again agitated with from 20 to 30 cc. of anhydrous petroleum ether and allowed to stand for one hour. After filtration into a weighed weighing-bottle with thorough washing of the filter paper, the residue was again dried and weighed. This gave the total weight of extracted lipoid material (fat plus fatty acid). Resolution was obtained by the use of alcohol-ether (3:1), and the fatty acids were titrated with alcoholic sodium hydroxide, phenolphthalein being used as an indicator. The weight of neutral fat was obtained by correcting for the glycerol set free in the hydrolysis of the fat.

Nitrogen, phosphorus and cholesterol contents were then determined on the fat plus fatty acid residue. The solution was made in anhydrous petroleum ether. The

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1. Berman, S. L.: Lipoid Histiocytosis (Niemann-Pick's Disease), Am. J. Dis. Child. **36**:102 (July) 1928.

2. Zelinsky, N. D., and Zinzadze, S. R.: Eine neue Methode der quantitativen Fettbestimmung in der tierischen Substanz und in ganzen Organismen, Biochem. Ztschr. **175**:335, 1926.

nitrogen content was determined on an aliquot portion by the micro-Kjelhahl method of Koch and McMeekin.[3] The phosphorus content was determined on another portion by oxidation, as described by Bloor,[4] and subsequent analysis for phosphorus by the inorganic phosphate method of Benedict and Theis.[5] The cholesterol content was determined on another portion by the gravimetric method of Windaus.[6] The water content was determined on the homogeneous, ground mass by the usual method.

Kerasin was tested for in the extract and found to be negligible. The method of Lieb[7] was used. The precipitate from the addition of mercuric chloride was too small to be considered.

The blood was analyzed for cholesterol by the method of Bloor, Pelkan and Allen;[8] for lecithin by the method of Bloor[4] and Benedict and Theis,[5] and for fatty acids by the method of Stewart and White.[9]

Tables 1 and 2 show several analyses from other workers, together with my results, as compared with analyses of normal organs. Table 3 shows the results of the examination of the blood as compared with normal blood.

COMMENT

Blood.—The cholesterol content was found to be 36 per cent above the average normal, or 22 per cent above the highest normal. The lipoid phosphorus content was found to be 85 per cent above the average normal, or 71 per cent above the highest normal. The fatty acids were found to be 58 per cent above the average normal, or 33 per cent above the highest normal. This analysis bears out previous reports as to a lipemia and hypercholesterolemia in Niemann-Pick's disease.

Liver and Spleen.—With my method of analysis, a comparison can not be made with previous work so far as weights of separate ether and alcoholic extracts and their constituents are concerned. However, a comparison can be made of such factors as total extractives, total nitrogen

3. Koch, F. C., and McMeekin, T. L.: A New Direct Nesslerization Micro-Kjeldahl Method, J. Am. Chem. Soc. **46**:2066, 1924.

4. Bloor, W. R.: Methods for Determining Phosphoric Acid in Small Amounts of Blood, J. Biol. Chem. **36**:33, 1918.

5. Benedict, S. R., and Theis, R. C.: A Modification of the Molybdic Method for the Determination of Inorganic Phosphorus in Serum, J. Biol. Chem. **61**:63, 1924.

6. Windaus, A.: Ueber die quantitative Bestimmung des Cholesterins und der Cholesterinesters in die einige normalen und pathologischen Nieren, Ztschr. f. physiol. Chem. **65**:110, 1910.

7. Lieb, Hans: Cerebrosidspeicherung bei Splenomegalie, Typus Gaucher, Ztschr. f. physiol. Chem. **140**:305, 1924.

8. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, J. Biol. Chem. **52**: 191, 1922.

9. Stewart, C. P., and White, A. C.: The Estimation of Fat in Blood, Biochem. J. **19**:840, 1925.

content and total cholesterol content. This seems to serve as well as the separate analysis of each fraction as given by other authors.

The difference between the analyses of the diseased organs is due, probably, to a difference between the ages of the patients and the dura-

TABLE 1.—*Analyses of Spleens in Cases of Lipoid Histiocytosis Compared with Analyses of Normal Spleens*

Author	Analysis in Gm. per 100 Gm. of Tissue						
	Total Lipoids	Fatty Acids	Lipoid Phosphorus	Lipoid Nitrogen	Cholesterol	Total Weight Gm.	Moisture, Per Cent
Niemann-Pick Spleens							
MacFate	13.2141*	0.6274	0.9163	2.0913	1.8887	122.9	78.44
MacFate	61.29†	2.91	4.25	9.7	8.76	.....	.....
Bloom and Kern: Arch. Int. Med. **39**: 456 (March) 1927.	68.841†	3.462	3.974	8.968	8.308	.....	76.7
Kramer: M. Clin. N. Amer. **11**: 905, 1928	57.5†	.....	.....	.....	.....	.....	74.3
Normal Spleens							
Bloom and Kern	22.851†	1.039	1.287	12.925	2.424	.....	81.4
Wahl and Richardson: Arch. Int. Med. **17**: 238 (Feb.) 1916	20.51†	.....	.....	.....	.....	.....	.....

* Wet; † dry.

TABLE 2.—*Analysis of the Liver in a Case of Lipoid Histiocytosis, and Comparison of Total Lipoids Found with Total Lipoids in the Normal Liver*

Components	Analysis in Gm. per 100 Gm. of Tissue		
	(MacFate)		(Wahl and Richardson)
	Niemann-Pick Liver		Normal Liver
Moisture	76.20 %		
Total weight	583.0 Gm.		
Total lipoids	12.2736*	51.57†	22.99†
Fatty acids	0.5974	2.51	.....
Lipoid phosphorus	0.9853	4.14	.....
Lipoid nitrogen	2.9702	12.48	.....
Cholesterol	1.7541	7.37	.....

* Wet; † dry.

TABLE 3.—*Comparison of Blood in a Case of Lipoid Histiocytosis with Normal Blood*

Components	Analysis in Mg. per 100 cc. of Blood	
	Niemann-Pick Blood	Normal Blood
Cholesterol	231	150 — 190
Lipoid phosphorus	24	12 — 14
Fatty acids	560	290 — 420

tion of the disease. However, all the analytic results reported in this study agree, in general, with those of other workers: a rise in total lipoid, fatty acid, lipoid phosphorus and cholesterol contents and a decrease in lipoid nitrogen content.

Histologically, the organs are seen to be filled with large, palely staining cells, which stain positively for complex lipoids, with a predominance of phosphatids in all organs but the abdominal lymph glands. This agrees well with the chemical analysis of the organs, as well as with the analysis of the blood, in which the lipoid phosphorus content is 71 per cent above the high normal.

From the work of Pick [10] it is evident that one is not dealing with a disease of the spleen alone. The lipemia and hypercholesterolemia, together with the presence of phosphatids, cholesterol and cholesterol esters in the cells of many organs, indicate that there is some disturbance of the lipoidal metabolism. The work of Aschoff [11] proved that the cells involved in this disease, as well as those in Gaucher's disease, are derived from the reticulo-endothelial system. There is evidence that the cells of this system participate in the elaboration of antibodies and in the metabolism of lipoid substances and cholesterol. At any rate, the lipoids are stored in the cells of the reticulo-endothelial system, especially in the spleen, liver, lymph glands and bone marrow, and also the suprarenal glands and thymus. When the cells of these organs have been filled, storage occurs in the specific parenchymal cells of various organs.[1]

The analysis confirms the separation of Gaucher's disease from Niemann-Pick's disease, the latter having the greatest deposition of phosphatids, cholesterol and cholesterol esters, of which the phosphatids predominate, and showing the absence of any considerable quantity of kerasin. Lipemia and hypercholesterolemia are present in Niemann-Pick's disease but absent in Gaucher's disease.

SUMMARY

The liver and the spleen from a case of Niemann-Pick's disease showed a great increase over the normal in lipoid content, especially phosphatids. This observation confirms previous work. The analysis serves to confirm the differentiation between Gaucher's disease and Niemann-Pick's disease.

10. Pick, L.: Ueber die lipoidzellige Splenohepatomegalie Typus Niemann-Pick als Stoffwechselerkrankung, Med. Klin. **23**:1483, 1927.

11. Aschoff, L.: Das reticulo-endotheliale System, Ergebn. d. inn. Med. u. Kinderh. **26**:1, 1924.

VASCULAR HYPOPLASIA IN STATUS LYMPHATICUS*

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Status lymphaticus is the name given to that combination of hereditary anomalies among which are certain peculiarities of external configuration, hyperplasia of the lymphoid tissues including the thymus gland, hypoplasia of the cardiovascular system, and other visceral defects of uncertain occurrence and irregular distribution. Status lymphaticus frequently terminates in sudden death, the cause of which is usually obscure.

For nearly two hundred years, the condition has been recognized to some extent. In the early part of the eighteenth century, Bichat [1] noted that sudden death from unknown cause is often associated with an enlarged thymus gland. But it was not until 1889 that Paltauf [2] of Vienna discovered that the enlarged thymus is only one of many hereditary anatomic imperfections which, when occurring in the same body, produce the condition known as status lymphaticus.

In 1905, Norris [3] of the Bellevue Hospital, New York City, began a series of observations on the peculiarities of external configuration in the bodies of persons brought into the city morgue dead from suicide or unknown cause. In 1909, he first made note of his observations in a letter to his old teacher, von Neusser of Vienna, who later published them together with some of his own work. This investigation begun by Norris has been continued by himself and his co-workers. In 1918, Symmers [4] summarized the work done up until that time. Among 5,652 routine autopsies, there had been 457 cases of status lymphaticus, or 8 per cent, which shows that the condition is much more frequent than is usually supposed.

The particular feature of status lymphaticus which will be discussed in this paper is the hypoplasia of the cardiovascular system. Although nearly every writer on status lymphaticus mentions the small heart and thin-walled blood vessels so frequently found, yet few have made any attempt to associate these observations with the sudden death of the patient. Nearly every surgeon of wide practice has seen one or more cases in which death occurred suddenly from no known cause during an operation. Every pathologist has occasionally performed an

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* From the Department of Pathology, University of Cincinnati College of Medicine.

1. Bichat, cited by Symmers, D.: Am. J. M. Sc. **156**:40, 1918.
2. Paltauf, A.: Wien. klin. Wchnschr. **2**:877, 1889; ibid. **3**:172, 1890.
3. Norris, C., in Johnson: Surgical Diagnosis, 1909, vol. 3, p. 705.
4. Symmers, D.: Am. J. M. Sc. **156**:40, 1918.

autopsy in a case of sudden death and has found absolutely nothing which he could conscientiously report as a cause of death. These mysterious cases frequently have the combination of characteristics described as status lymphaticus.

In the group of cases studied at the Bellevue Hospital the heart was unusually small in 51 per cent, a hypoplastic aorta was noted in 40 per cent, and the blood vessel wells were exceedingly thin in 26 per cent. Symmers [4] noted that "the cerebral vessels, particularly the arteries of the Circle of Willis and its branches, are often small in caliber and extremely thin and delicate. In the gross they are collapsed and translucent. Microscopically they are apparently deficient in the muscular coat which is definitely less developed than usual." Symmers then reported seven cases of status lymphaticus in which at autopsy the cause of death was found to be cerebral hemorrhage due to rupture of hypoplastic cerebral arteries. He also cited nine other cases of status lymphaticus in which miliary aneurysms not syphilitic in origin were found.

REPORT OF CASES

Recently at the General Hospital autopsies have been performed in two cases which may be added to the small series in the literature. A brief summary of these two cases follows:—

CASE 1.—A white woman, aged 32, with an essentially negative history, was well until three days before admission; at that time she complained of mild pain in the abdomen, which, according to her husband, did not incapacitate her in any way. Three days later, the husband found her lying on the floor in a stuporous state with frothy sputum about the mouth and breathing stertorously. Both eyeballs were protruding, and the left pupil was dilated. The patient was sent to the hospital, where she died a half hour following admission. The autopsy revealed only the following abnormalities: A large bilobed thymus weighing 35 Gm.; markedly enlarged lymph nodes, some of which could be palpated externally; skin fine-grained and almost hairless; heart valves unusually thin and of fine texture; thin-walled aorta; hyperplastic lymphoid tissue in the intestine and spleen, and a large blood clot weighing 50 Gm. in the region of the right lateral ventricle of the brain with softening of the surrounding brain tissue. The cause of death was cerebral hemorrhage.

CASE 2.—A colored man, about 30 years of age, brought to the hospital unconscious, was reported by the police to have been in an automobile accident. The only external evidence of injury was a small laceration on the forehead. The patient died one hour after admission. The clinicians thought he probably had a fracture of the skull, because of the signs of cerebral hemorrhage found on physical examination just before he died. At autopsy fracture of the skull was not found. There was not any extradural hemorrhage, but beneath the dura a large amount of blood covered both cerebral hemispheres. Many small hemorrhages were seen in the brain substance on cross section. The only other observations of note were: Persistent thymus; a thin-walled aorta with narrow lumen, and generalized hyperplasia of lymphoid tissue. The cause of death was cerebral hemorrhage.

In both cases the microscopic examination did not reveal notable pathologic changes in any of the organs other than generalized hyperplastic lymphoid tissue with large degenerating germinal follicles and multiple cerebral hemorrhages. Examination of the cerebral vessels with the routine hematoxylin-eosin stain showed them to be dilated and filled with blood. The smaller vessels had extremely thin walls and were frequently surrounded by zones of hemorrhage, which in some instances lay actually within the wall between the adventitia and the media. These might well be called miliary dissecting aneurysms. The larger vessels showed much less distinction than usual between arteries and veins, the muscular coat of the arteries being definitely under-developed.

The results with the van Gieson stain in these cases were striking. Many of the larger vessels in the brain, especially those in the regions of hemorrhage, contained little if any smooth muscle, their walls staining a deep pink. Sections of brain from other cases without status lypmphaticus present a much larger amount of smooth muscle in the walls of the vessels. The question arises as to whether arteries or veins or both are affected. In the two cases studied, both systems were apparently involved, but since it was so difficult to distinguish arteries from veins it would seem that the arteries probably showed a greater departure from normal, their deficiency in smooth muscle making them of about the same caliber as veins. Van Gieson stain on the vessels of abdominal and thoracic viscera did not reveal any marked abnormal appearances.

COMMENT

The consequences of such a deficiency in the musculature of the cerebral vessels can readily be imagined. Any sudden increase in blood pressure or other unusual strain on the cardiovascular system to which normal vessels could be readily accommodated might easily produce a catastrophe in vessels with this limited power of expansion and contractility. In looking over the so-called immediate causes of death given by various writers reporting cases of status lymphaticus in the literature, I find the following:

Anesthesia—local or general (many cases reported)
Setting up exercises
Wrestling and other athletic sports
Flogging
Sudden plunge into cold water—as in diving or bathing
Burns—not sufficient in themselves to be fatal
Mental and physical excitement
Electrical storm
Whooping cough
Crying spells

All these reports were of typical cases of status lymphaticus, in which autopsy did not reveal any other cause of death. Unfortunately, the autopsies in many cases did not include an examination of the brain.

It seems reasonably certain that in my two cases, and in a few cases reported by Symmers,[4] sudden death in persons with status lymphaticus was due to the bursting of hypoplastic cerebral vessels with resultant hemorrhage; the event initiating the fatality in each case seemed to be of minor importance, in fact, insignificant for a normal person. How many more unexplained deaths in cases of this type might be found to be due to the same cause if careful examination of the brain were to be made, I cannot say. I do not believe, however, that all deaths in status lymphaticus are on a cardiovascular basis. The cardiovascular defect is only one of many anatomic anomalies in these cases. I think that probably only a small percentage fall in this category; the others more likely are associated with that vague thing one hears so much about; namely, endocrine unbalance. From recent work of Marine [5] it would seem that the thymus gland is closely associated with the other glands of internal secretion.

In addition, there are cases of status lymphaticus which are unmistakably associated with anaphylaxis. Every asthma and hay-fever clinic has a disproportionate number of patients with status lymphaticus, and a certain number may die from sudden completion of a cycle of sensitivity. Symmers [4] suggested that the offending agents in such cases may be split proteins of the degenerating germinal lymph follicles so often seen in status lymphaticus.

Then there is one more type of patient that must be mentioned, namely, the person who commits suicide. Emerson,[6] in reporting 1,000 cases of attempted suicides, found 220 of the status lymphaticus type. Symmers suggested the possibility that congenital hypoplasia of the blood vessels in the brain may so alter the circulation as to influence mental poise.

SUMMARY

1. Two cases of status lymphaticus are reported in which the cause of death was cerebral hemorrhage resulting from hypoplasia of cerebral vessels.

2. The thinness of the vessel walls is accounted for by deficiency of musculature, there being no decrease in the thickness of intima and adventitia.

3. A corresponding decrease in musculature in vessels of other organs than the brain was not observed.

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5. Marine, D.: Status Lymphaticus, Arch. Path. **5**:661 (April) 1928.

6. Emerson, H.: Status Lymphaticus in Adults, Its Clinical Diagnosis and Its Importance, Arch. Int. Med. **13**:169 (Jan.) 1914.

Laboratory Methods and Technical Notes

THE MOUNTING OF MALFORMATIONS: A CONTRIBUTION TO THE ESTHETICS OF THE PATHOLOGIC MUSEUM *

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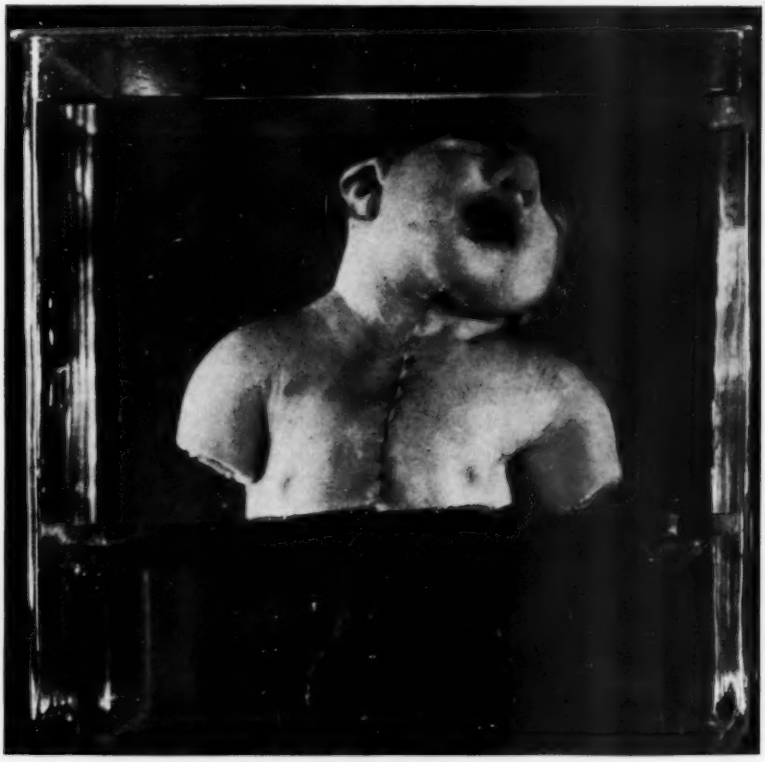
If a specimen is to be looked at for more than a few seconds, it must not be repulsive. Specimens of the internal organs are neither beautiful nor ugly in themselves; one is satisfied if they are mounted with well



Specimen described in text.

preserved color in a fitting jar. But when a specimen includes features of the body surface, especially the face, it enters the realm of deeply rooted esthetic feelings. Not only the layman and the student, but the old pathologist also, if he has not become too callous, will not view the head and the body of a new-born child with the same eyes with which he judges the merits of a specimen from the liver or the pancreas. For this reason, as the usual specimens of human malformations are horrid to look at, an attempt was made to find a more pleasing way of preserving an anencephalus.

* From the clinic of the Woman's Hospital.

The whole body was available. The only outer malformations present were those in the skull. The thorax was cut under the mamillae, and the arms were sawed off below the deltoid muscle, care being taken that the relative lengths of the stumps should be in accord with the lateral inclination of the head. The resulting shape was that of a portrait bust.

The base for this bust was cut from fragments of a broken table top, 1 cm. thick. The horizontal and vertical parts were glued together with Jeffery's marine yacht glue, the same as that used in the sealing of the jars. The chest cavity was wiped dry and filled with plaster of paris. This had two effects: it offset the buoyancy of the specimen, and it furnished a lower surface for fixation to the glass plate. The lower surface of the plaster was roughened, and several deep holes were cut out of it. Thus the specimen could be glued to the glass plate. The enlarged thymus was embedded in gelatin and fixed with gelatin to the anterior wall of the jar. The specimen together with the glass base was lowered into the jar by means of two pieces of string slung around the horizontal plate.

General Review

CARCINOMAS OF THE UTERINE CERVIX

THEIR HISTOLOGIC STRUCTURE, MALIGNANCY AND PROGNOSIS *

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Since Hansemann [1] brought the term "anaplasia" into existence, many attempts have been made to establish definite relations between the histologic structure of a carcinoma and its malignancy. While some workers (Borst,[2] Fischer,[3] Mayer,[4] Kuestner,[5] Plaut,[6] Walthard and von Franqué [7]) were unable to find any connections between these two factors, others believed from the results of their investigations that certain conclusions concerning the prognosis of a carcinoma can be drawn from an evaluation of the histologic symptoms. Hansemann [1] stated that a tumor which possesses the tendency to produce at an early stage metastases disseminated through the body usually shows a high degree of anaplasia, while a tumor, even of a locally considerable growth but without metastatic proliferations, has in general little anaplasia. He rarely observed exceptions to this rule and concluded that theoretically the degree of anaplasia is a fair indicator of the tendency of a tumor to form metastases. The result of Hertzler's studies [8] in this matter led him to believe that the degree of deviation of the cell type mainly decides the degree of malignancy. Herby [9] noted that a tumor is the more

* From the Department of Pathology, Loyola University School of Medicine and Mercy Hospital.

1. Hansemann: Studien über die Spezifität, den Altruismus und die Anaplasia der Zellen, Berlin, A. Hirschwald, 1893; Die mikroskopische Diagnose der bösartigen Geschwülste, Berlin, A. Hirschwald, 1902.

2. Borst: Die Klinik der bösartigen Geschwülste (Zweifel-Payr), Leipzig, S. Hirzel, 1925; Allgemeine Pathologie der malignen Geschwülste, Leipzig, S. Hirzel, 1924; Verhandl. d. deutsch. Gesellsch. f. Gynäk., 1923.

3. Fischer: Experimentelle Erzeugung von Tumoren, Klin. Wchnschr. **6**: 1535, 1927; Entwicklung der Geschwulstzelle, Klin. Wchnschr. **6**:1305, 1927; Ueber Krebs-embolien in Lungenarterien, Verhandl. d. Naturf. u. Ärzte, 1897; Verhandl. d. deutsch. Gesellsch. f. Gynäk., 1923.

4. Mayer: Verhandl. d. deutsch. Gesellsch. f. Gynäk., 1923.

5. Kuestner, quoted by Liegner: Beitr. z. Geburtsh. u. Gynäk. **18**:329, 1913.

6. Plaut, Alfred: The Relation Between the Histologic Picture and Prognosis of Tumors, Arch. Path. **3**:240 (Feb.) 1927; The Relation of Prognosis to the Histological Findings in Carcinoma of the Cervix, Surg. Gynec. Obst. **43**:450, 1926.

7. Von Franqué: Strahlenbehandlung der Genitalkarzinome, Strahlentherapie **21**:187, 1926; Die anatomische und histologische Einteilung der primären Uteruskarzinome, Med. Klin. **22**:1841, 1926.

8. Hertzler: A Treatise on Tumors, Philadelphia, Lea & Febiger, 1912.

9. Herby: Prognosis in Cancer, M. J. & Rec. **122**:509, 1925.

malignant the richer it is in cells. Unna,[10] who did not actually evaluate malignancy, recorded that carcinomas of the skin forming broad strands in which the mitotic figures are equally distributed are more malignant than those with styloid taperings at the ends of the epithelial pegs and mitoses predominantly in the peripheral layers of the carcinomatous cell nests. McCarty,[11] who investigated the relation of the stroma to the prognosis of carcinoma of the stomach, stated that the postoperative length of life was increased when the stroma was fibrotic or hyalinized and contained a marked lymphocytic infiltration. In spite of their scientific significance, these observations and statements do not have any great clinical value because they are not precise enough or are of such a general character that they cannot be applied to a single case so that definite conclusions can be drawn on the life expectancy. Broders [12] is responsible for the development of a method of evaluation of histologic malignancy through which the prognosis of a case can be expressed on a numerical basis. By dividing the carcinomas into four groups according to their degree of cellular differentiation, he attained a scale of percentages of mortality rising correspondingly to the decrease of differentiation in these four groups. He applied this system to carcinoma of different organs, such as the skin, lip, mouth, gallbladder and stomach, and stated that the same relation between histologic structure and prognosis existed in all of them. With the same point in view, Martzloff [13] grouped the primary solid carcinomas of the uterine cervix into three groups according to the predominating cell type (spindle cell carcinoma, transitional cell carcinoma and spinous cell carcinoma) and found that the number of cures was in direct relation to the maturity of the cell type present in three groups. Régaud,[14] who used a similar

10. Unna: Die Histopathologie der Hautkrankheiten, Berlin, A. Hirschwald, 1894.

11. McCarty: The Relation of Fibrosis and Hyalinization to Longevity in Cancer, J. Lab. & Clin. Med. **8**:42, 1922; Prognostic Factors in Cancer, Ann. Clin. Med. **2**:244, 1924. McCarty and Mahle: Relation of Differentiation and Lymphocytic Infiltration to Postoperative Longevity in Gastric Carcinoma, J. Lab. & Clin. Med. **6**:473, 1921.

12. Broders, A. C.: Carcinoma, Grading and Practical Application, Arch. Path. **2**:376 (Sept.) 1926; Cancer's Selfcontrol, M. J. & Rec. **121**:133, 1925; Squamous Cell Epithelioma of the Skin, Ann. Surg. **73**:141, 1921; Squamous-Cell Epithelioma of the Lip, a Study of Five Hundred and Thirty-Seven Cases, J. A. M. A. **74**:656 (March 6) 1920; Epitheliomas of Cavities and Internal Organs of the Head and Neck, Arch. Surg. **11**:43 (July) 1925; Carcinoma of the Neck, Types and Degrees of Malignancy, Am. J. Roentgenol. **17**:96, 1927.

13. Martzloff: Carcinoma of the Cervix Uteri, Bull. Johns Hopkins Hosp. **40**:160, 1927.

14. Régaud: Strahlentherapie der Zervixkarzinome, Fortschr. a. f. Geb. d. Röntgenstrahlen. **35**:288, 1926.

classification, reported similar observations. Greenough,[15] the most recent contributor to this subject, studied carcinomas of the breast. He divided these tumors into three groups, low, medium and highly malignant carcinomas, according to their degree of differentiation and amount of anaplasia calculated on a percentage basis. The degree of malignancy as represented in these three groups showed a definite relationship to the percentage of cures obtained in the three groups.

Commenting on the three methods just described, the result of which, as I believe, proves the existence of a correlation between the histologic structure and the prognosis of a carcinoma, I must state that each one has imperfections that impair their usefulness and general application. First, in regard to the method employed by Broders,[12] while there can be no doubt of the correctness of his observations, which were obtained not only on by far the largest number of cases but on carcinomas of different organs, in my opinion there remains one decided defect of his method, that is, the lack of any available detailed data of his technic. On account of this fact, a correct and precise duplication of his method and a substantiation of his results by other workers are not possible if they are not in the position of procuring the necessary information by direct personal cooperation with Broders. Concerning the method used by Martzloff,[13] subsequent investigators failed to corroborate his observations to their full extent (Plaut,[6] Schmitz and Hueper[16]). I am not able to explain this discrepancy, but I may point out one fact: Any evaluation of histologic malignancy which is based on only one factor is incomplete and therefore incorrect. A carcinoma is not sufficiently characterized by the cell type alone; the amount of anaplasia has to be taken into consideration too. The information given by Greenough[15] in regard to the technic employed is somewhat more thorough, but he also fails to give enough technical data to enable one to make an exact duplication of his work.

Recognizing the apparent defects of the three methods mentioned but using them as a base for my own investigations, I developed a technic of

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15. Greenough: Varying Degrees of Malignancy in Cancer of the Breast, J. Cancer Research **9**:453, 1925; Carcinoma of the Breast, Am. J. Roentgenol. **16**:439, 1926.

16. Schmitz; Hueper and Arnold: The Significance of the Histological "Malignancy Index" for the Prognosis and Treatment of Carcinomata of the Cervix Uteri, Am. J. Roentgenol. **16**:30, 1926. Hueper and Schmitz: Der "histologische Malignitätsindex" und seine Bedeutung für die Prognose und Behandlung der Cervixcarcinome des Uterus, Strahlentherapie **24**:660, 1927. Schmitz: The Treatment of the Inoperable Cervical Carcinomata with Measured Doses of X-Rays and Radium Based on Microscopic Examinations: The Five Year End-Results, Am. J. Obst. & Gynec. **9**:644, 1925; Relation of Degree of Histologic Malignancy to Prognosis and Treatment of Carcinoma of Uterine Cervix, Radiology **9**:322, 1927.

evaluation of histologic malignancy in which these imperfections were eliminated to a wide extent by the introduction of nine factors which are recognized as characteristics of differentiation and anaplasia and which were evaluated on a percentage basis. The sum of the results translated into numerical values represented the "histologic malignancy index." In the report of these studies,[16] I emphasized my belief that only through a careful consideration of numerous factors would real progress in this field of work be made. Following this conception, I have reexamined the material used for the first paper and have increased the number of factors from nine to twenty. The results of these investigations are contained in the present communication.

The twenty factors evaluated represent histologic qualities of the cells and of the structure of the parenchyma and stroma of the cervical carcinomas of the uterus. For the descriptions of these histologic features, several terms are employed in the use of which sufficient discrimination is not always observed. The expressions referred to are anaplasia, differentiation, maturity, ripeness and embryonicity. They are frequently used as synonyms in spite of the fact that they designate different properties of a carcinoma. It will therefore be advisable to give precise definitions of these terms to avoid any confusion of their meaning. The term "anaplasia" refers to the pathologic deviations of the cytoplasm and the nuclei of carcinoma cells in their appearance, structure and interrelation from the same qualities of normal, adult as well as embryonic, cells of the same type. According to Ewing,[17] the amount of anaplasia present in a tumor indicates the degree to which the process is freed from growth restraints and the control of the organization. Irregularity in size and shape of the cells and the nuclei (pleomorphism), distinctness in outline of the cells, chromatism of the cytoplasm and the nuclei, number and irregularity of the mitoses and infiltrative growth of the carcinoma cells are the characteristics by which the amount of anaplasia may be estimated. Differentiation defines the degree of the cellular and structural development of a carcinoma as apparent from a comparison with developmental stages present in the corresponding normal tissue. It is evident from these explanations that anaplasia and differentiation designate different qualities of a carcinoma. The terms ripeness, maturity and embryonicity also describe stages of cellular and structural development and may therefore be used to designate different degrees of differentiation.

In the present communication, an elaborate attempt is made to determine histologic malignancy through the evaluation of twenty factors characterizing the degree of differentiation and anaplasia of the tumor

17. Ewing: Neoplastic Diseases, ed. 2, Philadelphia, W. B. Saunders Company, 1922.

and the condition of the stroma. The list of the factors composing the improved "histologic malignogram" is as follows:

(1) Special cell type of carcinoma.
(2) Nucleocytoplasm coefficient.
(3) Irregularity in size of cells.
(4) Irregularity in shape of cells.
(5) Distinctness in outline of cells.
(6) Chromatism of cytoplasm.
(7) Functional activity of cells.
(8) Irregularity in size of nuclei.
(9) Irregularity in shape of nuclei.
(10) Chromatism of nuclei.
(11) Hyperchromatism of nuclei.
(12) Number of mitoses and prophases.
(13) Irregularity of mitoses.
(14) Number of "pencil cells."
(15) Infiltrative growth of cells.
(16) General type of carcinoma.
(17) Character of stroma.
(18) Vascularity of stroma.
(19) Type of cellular infiltration of stroma.
(20) Amount of cellular infiltration of stroma.

DEFINITIONS AND ARGUMENTS

(1) *Special Cell Type of Carcinoma.*—The carcinomas of the uterine cervix were divided into two main groups, the primary solid carcinomas and the glandular carcinomas. Each of these main groups was subdivided into four subgroups according to the predominant type of cell and the structural appearance respectively or, in other words, according to their degree of differentiation. This classification is based on the general structure and maturity of the cell type and does not refer to the cellular origin of the particular type of malignant growth. Histogenetic points of view did not enter in this classification. A detailed description and photomicrographs of the different cell types were published in a previous paper.[16] The carcinomas were classified as:

A. Primary solid carcinomas.
  (1) Spinous cell carcinoma with cornification.
  (2) Spinous cell carcinoma without cornification.
  (3) Round cell carcinoma.
  (4) Spindle cell carcinoma.

B. Glandular carcinomas.
  (1) Malignant adenoma.
  (2) Papillary and gelatinous adenocarcinoma.
  (3) Adenocarcinoma simplex.
  (4) Solid adenocarcinoma.

The guiding idea of this arrangement of the cervical carcinomas was a utilization of the clinical observation that the potential malignancy of a carcinoma increases with the decrease of the degree of differentiation.

The evaluation of this factor was carried through in the following manner: Carcinomas of subgroups 1 were evaluated with two points, those of subgroups 2 with four, those of subgroups 3 with six and those of subgroups 4 with eight points.

(2) *Nucleocytoplasm Coefficient.*—In the evaluation of the nucleocytoplasm coefficient, an estimation of the relative number of those cells which had a rather large nucleus but a relatively small amount of cytoplasm and an absence of degenerative changes in the cells was made. The nucleocytoplasm ratio of these cells approaches the value one. If 10 per cent or less of such cells were among the carcinoma cells, one point was counted; if 20 per cent were present, two points, if 30 per cent were present, three points and if more than 30 per cent were present, four points were counted. The significance of the nucleocytoplasmatic ratio is known through the thorough investigations of Sokoloff [18] and Robertson.[19] Sokoloff concluded that cancer cells with an elevated nucleocytoplasmatic ratio possess a much increased vital activity. Cullen [20] as well as Lubarsch [21] attributes special infiltrative power to carcinomas composed of small cells, which usually have a relatively small cytoplasm in regard to the size of the nucleus.

(3 and 4). *Irregularity in Size and Shape of Cells.*—The average size and shape of the tumor cells were studied. Deviations from this size and shape present in from 40 to 50 per cent of the cells were evaluated with four points; in from 30 to 40 per cent with three points, in from 20 to 30 per cent with two and below 20 per cent with one point. Areas around necroses and degenerations were excluded from an estimation on account of the changes in size and shape of the cells produced by degenerative processes. The diffuse irregularity in the same cell strand was considered as more significant than the presence of cells of different size and shape in different nests and parts of the section. Irregularities in size and shape of the tumor cells were interpreted as signs of anaplasia.

(5) *Distinctness in Outline of Cells.*—Distinct outlines present in 75 per cent or more of the cells were counted with one point, distinctness present in from 50 to 75 per cent with two, in from 25 to 50 per cent with three and below 25 per cent with four points. Indistinct outlines of cells and occurrence of syncytium-like masses were regarded as evidence of anaplasia (Blair-Bell [22]).

18. Sokoloff: Recherches cytologiques et biologiques consacrées au problème du cancer, Vienna, Emil Haim & Co., 1926.

19. Robertson: The Nucleo-Cytoplasmic Ratio and Cancer, J. Cancer Research **8**:292, 1924.

20. Cullen: Cancer of the Uterus, 1909.

21. Lubarsch, quoted by Plaut (footnote 6, second reference).

22. Blair-Bell: Theory and Practice in Relation to Treatment of Cancer, Lancet **1**:687, 1926; Treatment of Malignant Diseases with Lead, Lancet **1**:537, 1926.

(6) *Chromatism of Cytoplasm.*—If the majority of cells had an almost unstained cytoplasm while the connective tissue was well stained with pink, four points were counted. If the cytoplasm was only slightly stained with pink, three points were evaluated; a cytoplasm moderately stained with pink was counted with two points and a distinctly pink one with one point. This factor was evaluated from the point of view that young cells and those in preparation of mitosis have a loose cytoplasm which does not readily take the eosin stain. Differentiation and proliferative activity were therefore estimated by this factor.

(7) *Functional Activity of Cells.*—Keratin granules and droplets of mucus in the cells were regarded as evidence of functional activity. Functional activity present in from 0 to 10 per cent of the tumor cells was evaluated with four points; in from 10 to 20 per cent with three, in from 20 to 30 per cent with two and in more than 30 per cent with one point. This factor was included with the consideration that as a rule the proliferative activity decreases in as much as the functional activity increases. Moreover, the cells having a special function represent a higher differented cell type than those without any apparent function.

(8 and 9) *Irregularity in Size and Shape of Nuclei.*—The same points of view and the same percentages were used in the evaluation of this factor as for that in regard to the irregularity in size and shape of the cells. This factor was considered as evidence of anaplasia.

(10) *Chromatism of Nuclei.*—If the majority of the tumor cells had nuclei that were almost as dark as the nuclei of lymphocytes, four points were counted; if they were somewhat paler, three points; if they were distinctly paler, two points and if they were very pale, one point. The relative chromatism of the nucleus was regarded as an indicator of the vital energy present in the cell. Cells with a faintly stained nucleus were considered as vitally weaker than those with a distinctly stained one.

(11) *Hyperchromatism of Nuclei.*—If 20 per cent or more of the nuclei were as distinctly dark stained as the nuclei of lymphocytes, the factor was evaluated with four points; if from 15 to 20 per cent were hyperchromatic, three points were counted; if from 10 to 15 per cent two points and if hyperchromatic nuclei were present in less than 10 per cent, one point was counted. Hyperchromatic nuclei in tumor cells were considered as expressions of anaplasia.

(12) *Number of Mitoses and Prophases.*—Mitoses and prophases were counted separately but considered together. Ten fields were counted with oil immersion (with a magnification of 1050) giving an actual count of the mitotic figures on which to base the estimate of the proliferative activity of the carcinoma examined. In glandular carcinomas and sometimes also in primary solid carcinomas in which it was

found impossible to examine complete fields of tumor cells, a corresponding larger number of fields was counted to compensate for the empty spaces of the glandular lumina or the stroma respectively present in the fields. In case 20 or more mitoses and prophases were counted, a value of four was given; from 15 to 19 mitoses and prophases were counted with three points; from 10 to 15 with two and below 10 with one point. Mitoses and prophases were regarded as the visible evidence of the proliferative activity of a tumor. The larger the number of mitoses and prophases present in a tumor the faster will be its increase in malignant cells. Granting that a part of the multiplication of the tumor cells will take place by amitosis, the inclusion of the prophases which represent a shortened type of mitotic cell division without spindle formation and disappearance of the nuclear membrane, a process of cellular multiplication similar to amitosis was considered as a circumstance that will lessen the importance of an apparent defect of my method, neglecting the amitotic process. Hansemann [1] stressed the significance of the number of mitoses for the degree of malignancy. Palugyay [23] found prophases to be frequent in immature carcinomas of the cervix. Unna [10] attached some importance to the distribution of the mitoses in the tumor tissue, as mentioned before. Sokoloff [18] observed that mitoses are sometimes more frequent near degenerative foci, an observation that agrees with my own. Decomposition products seem to act as a stimulus on the proliferative activity of the tumor cells. Ewing [17] stated that mitotic figures are more often observed in rapidly growing tumors than in slowly growing ones, and Oertel [24] noted the lack or scarcity of mitoses in some fast growing neoplasms. Plaut [6] asserted that the number of mitoses could be taken as an index of the loss of functional differentiation because they interfere more markedly with the function of the dividing cell than the amitoses do. From this statement, it may appear that the mitotic process contributes more to the malignancy than the amitotic one.

(13) *Irregularity of Mitoses.*—If less than 10 per cent of the mitoses present were pathologic, one point was counted; if from 10 to 20 per cent, two points; if from 20 to 30 per cent, three points, and if above 30 per cent, four points. The percentage was determined usually from at least ten mitoses seen. Irregularity in shape and size of mitoses was regarded as evidence of anaplasia. Hansemann [1] emphasized the significance of the atypical forms of mitoses for the degree of malignancy, and Palugyay [23] reported that knotty and asymmetrical mitoses are espe-

23. Palugyay: Reifestadien des Karzinoms und Zellteilung, Ztschr. f. Krebsforsch. **22**:251, 1925.

24. Oertel, Horst: General Pathology, New York, Paul B. Hoeber, 1921, pp. 357.

cially frequent in immature carcinomas, while multipolar and giant mitoses are found more often in mature ones.

(14) *Number of "Pencil Cells."*—The complete absence of "pencil cells" was evaluated with four points. Their presence in a small number was counted with three points, a moderate number of them with two points and the occurrence of numerous pencil cells with one point. These cells were first described by Lahm.[25] He reported that in carcinomas of the uterine cervix which were cured slender cells with dark staining nuclei were present in the carcinomatous cell nests. According to Lahm, they originate from carcinoma cells but possess the quality of destroying normal carcinoma cells. Fibroblasts and capillaries follow these peculiar cells and complete their work of destruction. He called them "pencil cells" on account of their shape.

(15) *Infiltrative Growth of Cells.*—If the outlines of the cell strands were in general well defined, one point was counted. Exceptions to this condition present in from 25 to 50 per cent of the cell nests were evaluated with two points. Diffuse infiltrative growth of the tumor cells into the stroma without distinct demarcation in from 50 to 75 per cent was evaluated with three points and the predominance of this type of growth in more than 75 per cent with four points. The leading point of view of this classification and evaluation was as follows: Carcinomas with well defined cell strands were regarded as less malignant than those with diffuse infiltrative growth. Carcinomas with well defined cell nests possess apparently more expansive than infiltrative proliferative qualities, because the body seems to be able to wall off the neoplastic growth temporarily. Kromayer's [26] observations may be mentioned here in support of this conception. He saw indistinct demarcation between cell nests and stroma; this was especially marked in rapidly growing experimental tar cancers and was found more frequently in the periphery of the tumor in which young, actively growing strands were present than in the center with its older cell nests. Nicod's [27] opinion that the stroma is an element of spontaneous reaction against the presence and growth of the neoplasm may be mentioned too. He distinguished between three types of stroma formation: 1. The stroma reaction precedes the growth and sets up a connective tissue barrier. 2. Synchronous production of a connective tissue barrier is present which is not formed early enough to

25. Lahm: Die Bedeutung der mikroskopischen Untersuchung für die Behandlung und Prognose des Collumkarzinoms, Ergebn. d. Strahlenforsch. **1**: 556, 1925; Die Prognose des bestrahlten Uteruscarcinoms im Lichte der mikroskopischen Untersuchung, Strahlentherapie **25**:22, 1927.

26. Kromayer: Zur Histiogenese des Krebsstromas, Ztschr. f. Krebsforsch. **24**:1, 1926.

27. Nicod, J. L.: Stroma Reaction in Neoplasms, Foreign Letters, J. A. M. A. **88**:581 (Feb. 19) 1927.

oppose effectively the extension of the new-growth. 3. A tardy stroma reaction chokes the tumor in the center but allows the peripheral neoplastic elements to proliferate. Schiller [28] described carcinomas of the uterine cervix in which any infiltrative growth was lacking. The carcinoma cells covered the portio as a well demarcated coat, without forming any processus into the underlying connective tissue. Schiller believed that the absence of any infiltrative growth is due to a defensive reaction of the connective tissue. He thought that this condition represents the first stage of the carcinomatous growth, which is followed by the second or infiltrative stage as soon as the defensive qualities of the connective tissue are broken down.

(16) *General Type of Carcinoma.*—If 75 per cent or more of the tumor was parenchyma and 25 per cent or less was stroma, four points were evaluated. If the ratio between parenchyma and stroma was from 50 to 75 per cent parenchyma and from 25 to 50 per cent stroma, three points were counted; if it was from 25 to 50 per cent parenchyma and from 50 to 75 per cent stroma, two points were counted and if 25 per cent or less parenchyma and 75 per cent or more stroma were present, one point was noted. The classification and evaluation of the parenchyma-stroma ratio was undertaken from the point of view that cellular carcinomas, medullary carcinomas, are in general more malignant than those with a high amount of stroma.

(17) *Character of Stroma.*—A loose connective tissue stroma was evaluated with four points, a moderately loose one with three points, a predominantly fibrous one with two points and a fibrous one with hyalinizations, one point. A loose connective tissue stroma was regarded as a factor facilitating the spreading of the tumor cells (Greil [29]), while the fibrotic stroma augments the local resistance of the body against the invasion of the tumor cells. General clinical observations and the investigations of McCarty [11] may be mentioned in corroboration of this conception. The character of the stroma in the periphery of the tumor in which the actual relation between parenchyma and stroma is undisturbed has to be regarded as more significant than its character in the center of the tumor in which fibrosis and hyalinization may have taken place as the result of an aging process (Greenough,[15] Kromayer [26]) or of a reactive and compensatory connective tissue proliferation with subsequent scar formation, due to necrosis of tumor tissue. Secondary alterations of the original tumor structure, as evidenced by a fibrotic and hyalinized stroma containing tumor cells with regressive changes, may

28. Schiller: Untersuchungen zur Entstehung der Geschwülste, Virchows Arch. f. path. Anat. **21**:359, 1926.

29. Greil: Grundfragen der Methodik der aetiologischen Krebsforschung, Verhandl. d. deutsch. path. Gesellsch. **21**:359, 1926; Das Krepsproblem, 1925.

produce a picture resembling a scirrhous carcinoma. A true scirrhous carcinoma is a primary condition representing the result of the reaction between the destructive action of the tumor cells and the defensive action of the stroma. Recent investigations of Bierich [30] may be noted in this connection. Bierich, who worked with tar carcinomas, observed a swelling and subsequent lysis of the collagenous fibrils of the connective tissue before the invasion of the tumor cells into the stroma took place. Simultaneously, and following the alteration of the collagenous fibrils, "elastic fibrils" were formed in the intercellular spaces of the connective tissue from an exudative material. Then, also, this dense elastic network started to swell and to be dissolved, and at the same time the invasion of the carcinoma cells began. Bierich believed that the lytic process is the result of the production of lactic acid by the tumor cells. From these observations, it is apparent that a loosening of the stroma facilitates the spreading of the carcinoma cells (Lewis [31]).

(18) *Vascularity of Stroma.*—A highly vascular stroma was evaluated with four points, a moderately vascular one with three points, a slightly vascular one with two points and a stroma with scanty vessels, with one point. This evaluation was based on the consideration that the vessels are to a great extent substantial in the spreading, especially in the metastatic proliferation of a malignant growth (Greil [29]). The preformed channels of the vessels and lymphatics offer the way of least resistance to the growing tumor cells (Rubens-Duval [32]).

(19) *Type of Cellular Infiltration of Stroma.*—A predominantly eosinophilic infiltration of the stroma was evaluated with one point, an infiltration composed mainly of lymphocytes and plasma cells and eventually also of a few eosinophilic leukocytes, with two points, an infiltration consisting of lymphocytes, plasma cells and a few neutrophilic leukocytes, with three points and an infiltration with a predominance of neutrophilic leukocytes with four points. The favorable significance of the eosinophilic infiltration in regard to the prognosis is unanimously recognized (Fluhmann,[33] Schoch,[34] Lahm,[25] Régaud,[14] Rubens-Duval,[32]

30. Bierich: Vorgänge bei Einwachsen der Krebszellen, Klin. Wchnschr. **6**: 789, 1927; Ueber die Bedeutung des Bindegewebes bei der experimentellen Krebsbildung, Virchows Arch. f. path. Anat. **239**:1, 1922.

31. Lewis, W. C. M.: The Nature of Malignant Neoplasms and Treatment of the Disease with Lead, Brit M. J. **2**:920 and 937, 1926.

32. Rubens-Duval: Les réactions locales et générales de l'organisme à l'égard du cancer, Congrès du Cancer, 1923; Processus histologique de la défense spontanée de l'organisme contre le cancer, Ann. d. méd. **1**:75, 1914.

33. Fluhmann: Carcinoma of the Cervix Uteri; a Clinical and Pathological Study, Am. J. Obst. & Gynec. **13**:174, 1927.

34. Schoch: Ueber die lokale Eosinophilie bei Karzinom, Zentralbl. f. Gynäk. **45**:2895, 1926.

Laborde,[35] Boehm and Zweifel[36]). Alyakriskiy[37] noted that eosinophils are frequent in cancer tissue but absent in nonmalignant tumors, with the exception of those of the skin and polypous growths. He concluded from his observations that the presence and the number of eosinophils depend on the amount of disintegrating tissue, the resorption of the resulting substances and their chemical character. According to the conclusions of Alyakriskiy and clinical observations, the eosinophils may represent protective elements of the body against the toxic decomposition products of the carcinoma cells. Their presence in a large number will act most favorably when an acute destruction of large masses of tumor cells takes place, such as occurs after radiation of carcinomas. The opinions about the significance of the lymphocytes and plasma cells in the stroma are still divided. While Dupont and Leroux,[38] Renaud,[39] Itchikawa and Baum,[40] Wood,[41] Rubens-Duval,[32] Roussy and Leroux,[42] Sittenfield,[43] Régaud,[14] Woglom,[44] Hansemann,[1] Borst[2] and others did not recognize any specific action of the lymphocytes against the tumor cells, Sokoloff,[18] Alter,[45] Darier,[46] Russ and Chambers,[47] Scott and

35. Laborde: Conception de la radiosensibilité des tissus, J. de radiol. et d'électrol. **8**:289, 1924.

36. Boehm and Zweifel: In wieweit kann man heute aus mikroskopischen Befunden eine Prognose für die Bestrahlung des Uteruskarzinoms stellen? Zentralbl. f. Gynäk. **50**:30, 1926.

37. Alyakriskiy: Tissue Eosinophilia in Tumors, Russk. Klin. **6**:609, 1926; abstr. J. A. M. A. **88**:1690 (May 21) 1927.

38. Dupont and Leroux: Importance du stroma pour les pronostic des cancers du sein et spécialement des cancers irradiés, Bull. et mém. Soc. médic. Paris, 1923, vol. 3.

39. Renaud: Les cancers et leurs complications, 1927.

40. Itchikawa and Baum: Rapid Production of Cancer in Rabbits by Coal Tar, J. Cancer Research **9**:85, 1925.

41. Wood, F. C.: Immunity in Cancer, J. A. M. A. **85**:1039 (Oct. 3) 1925.

42. Roussy; Laborde; Leroux and Peyre: Sur les modifications du sang au cours du traitement du col de l'utérus par les rayons X, Compt. rend. Soc. de biol. **86**:200, 1922; Réactions locales et générales de l'organisme au cours du traitement du col de l'utérus par les rayons X, Bull. de l'ass. franç. pour l'etude du cancer **9**:8, 1922.

43. Sittenfield: Significance of Lymphocytes in Cancer, J. Cancer Research **2**:151, 1917; Further Studies on Importance of Lymphocytes in Cancer Immunity, J. Cancer Research **4**:57, 1919.

44. Woglom: The Lymphnodes in Immune Rats, J. Cancer Research **4**:44, 1919; Immunity to Transplantable Neoplasms, Proc. Pan. Am. Sc. Congress, Washington, 1917, vol. 10, p. 362.

45. Alter: Histological Changes in Squamous Cell Carcinoma of the Cervix of the Uterus After Radiation, J. M. Research **40**:241, 1919; Histological Changes of the Different Types of Carcinoma After Exposure to Radium Rays, J. M. Research **41**:439, 1920.

46. Darier: Précis de dermatologie, Paris, Masson et Cie, 1923.

47. Russ and Chambers: Growth and Division of Cell as Affected by Radiation, Science Prog. **13**:605, 1918.

Mottram,[48] Ewing,[17] McCarty and Mahle,[11] Murphy,[49] Tyzzer,[50] Broders,[12] Holl [51] and others believed that a lymphocytic infiltration is an antiblastic reaction of the body. Sokoloff [18] concluded, as a result of his experiments, that the lymphocytic infiltration induced by roentgen-ray treatment in the subcutaneous tissue renders this tissue unsuitable for the implantation of carcinoma tissue. Teilhaber [52] claimed to have shown by his experiments that lymphocytes can actively destroy carcinoma cells. Murphy [49] believed that the lymphocytic infiltration is an index of the resistance of the body and a necessary factor in cancer immunity. In rapidly growing carcinomas, the absence of any cellular infiltration of the stroma is sometimes striking. In such cases, either the body did not have sufficient time or it was too weak to react with a lymphocytic infiltration. Concerning the significance of the leukocytic infiltration, the opinion prevails that an infiltration of the stroma with neutrophilic leukocytes is an unfavorable sign, because the neutrophilic leukocytes are evidence of an acute inflammatory process accompanied by hyperemia and edema, processes facilitating the spreading of the tumor. But I have found one exception to this rule. The presence of leukocytes in carcinoma cells is probably a favorable sign, being evidence of an active destruction of the tumor cells by elements of the body (anti-cancerous phagocytosis of Babes,[53] Minoflet and Schrumpf-Pierson [54]).

(20) *Amount of Cellular Infiltration of Stroma.*—A dense cellular infiltration of the stroma was evaluated with one point, a moderate one with two, a scanty one with three and a very scanty one with four points. In this grouping I followed and applied the considerations given for factor 19.

TECHNIC

Tissue removed for the determination of the index of histologic malignancy should not be excised, if possible, from the very periphery of the tumor in which the tumor cells are exposed to the effect of mechanical influences of

48. Scott and Mottram: Experimental Studies with Small Doses of X-Ray, Lancet **1**:692, 1919.

49. Murphy and Morton: The Lymphocyte as Factor in Natural and Induced Resistance to Transplanted Cancer, Proc. Nat. Acad. Sc., Baltimore **1**:435, 1915.

50. Tyzzer: Tumor Immunity, J. Cancer Research **10**:239 and 161, 1916.

51. Holl: Beitrag zur Frage des Zusammenhanges zwischen Blutbild und Prognose beim bestrahlten Gebärmutterkrebs, Arch. f. Gynäk. **127**:708, 1926.

52. Teilhaber: Zur Frage der Carcinome, München. med. Wchnschr. **74**: 242, 1927; Biologische Behandlung des Karzinoms, ibid. **74**:1087, 1927.

53. Babes: The Defensive Process of Tissues Against Cancer, Bull. de l'ass. franç. pour l'étude du Cancer **15**:381, 1926.

54. Minoflet and Schrumpf-Pierson: Réaction du sang et des tissus sains ou pathologiques sous l'influence des rayons X, Arch. d'electric. med. **489**:490, 1923.

the newly invaded tissue nor from the center of the tumor in which the original structure of the neoplasm is frequently altered. The excision of ulcerated parts and those containing extensive necroses is also not advisable and should be avoided for similar reasons. The removed piece of tissue should be placed directly into 4 per cent formaldehyde solution and should be of moderate size to enable a quick and equal penetration of the fixating fluid. Such a management of the excised tissue will prevent postoperative regressive changes such as edema, fatty degeneration and necrosis, processes which may cause errors in the interpretation of the microscopic sections. The number of the mitotic figures does not vary in the tissue fixed in the first twenty-four hours after removal, according to the investigations of Newton Evans.[55] If these rules are observed, the section to be examined may be taken from any part of the tumor. Variations of the cellular and structural conditions in different parts of the tumor are not so considerable that they would influence the end-result, according to observations of Lahm[58] and Hueper.[16] Paraffin sections that have been carefully prepared and stained should be used exclusively for this purpose. Frozen sections are unfit for this type of work on account of the frequent distortions and other alterations produced by the freezing process in the cellular and general structure of the tissue interfering with a proper and correct interpretation of the histologic symptoms. Each factor has to be evaluated separately. Any attempt to evaluate several factors at a time will lead only to incorrect estimations. The sections to be examined must contain a sufficient amount of carcinomatous tissue to enable the making of a fair evaluation. The clinical information accompanying the tissue should not include any data that could prejudice the pathologist in his estimations, a standpoint that was also stressed by Broders.[12]

RESULTS OF STUDY

One hundred and twenty-two carcinomas of the uterine cervix were examined by means of the rules mentioned, as far as this was possible with a material not specially prepared for this work. The patients were admitted during the years 1922 to 1925, inclusive. Table 1 presents the 122 cases from a purely pathologic standpoint.

The influence of the cell type on the malignancy index is evident from this compilation when the average malignancy indexes are considered, but at the same time the inexactness of a method which would base the prognosis exclusively on the cell type becomes apparent when the recorded variations of the malignancy indexes among the carcinomas of the same cell type are studied. The clinical value of the improved histologic malignancy index was tested by a comparison of the malignancy indexes obtained with the clinical end-results. The clinical end-results were graded by Schmitz[16] in the previous paper in the following manner: Clinical end-result: (1) the patient was free from symptoms and showed an anatomic healing three years after the beginning of the treatment; (2) the patient lived from two to three years after the beginning of the treatment; (3) the patient lived from one to two years after

55. Evans, Newton: Mitotic Figures in Malignant Tumors as Affected by Time Before Fixation of Tissue, Arch. Path. **1**:894 (June) 1926.

treatment was started; (4) the patient lived up to one year. The end-results were known in forty-eight of the 122 patients examined. Carcinomas which had become generalized when the treatment was started were not included in this group on account of their invariably infaust prognosis. To ascertain the relation between the clinical end-results and the malignancy indexes, the scale of the malignancy indexes which extends from 22 to 84 was divided into four sections. Section 1 included the malignancy indexes between 22 and 39; section 2, those between 40 and 54; section 3, those between 55 and 69, and section 4, those between 70 and 84. There was no case with a known end-result in the first section. In the second section thirteen cases were recorded with an end-result 1 in 61.54 per cent. In the third section in which twenty-eight patients were examined an end-result 1 was obtained in 28.57 per cent, while in the last section with seven cases an end-result 1 was noted in 0 per cent. A diagram (chart 1) in which the percentages of end-result 1 are recorded on the abscissa and the malignancy indexes on the coordinate demonstrates the interrelation between histologic struc-

TABLE 1.—*Pathologic Data of Cases*

Special cell type 2: 3 cases, average malignancy index 48.7 ranging from 45 to 55
Special cell type 4: 39 cases, average malignancy index 51.8 ranging from 34 to 70
Special cell type 6: 54 cases, average malignancy index 58.4 ranging from 40 to 71
Special cell type 8: 26 cases, average malignancy index 65.1 ranging from 45 to 79

ture represented by the malignancy index and the prognosis more strikingly than the numerical values will do it. The "malignancy line" resulting from a connection of the points which represent the percentages of end-result 1 in the different sections is almost a straight line running from 0 to 100 per cent.

END-RESULT AND STROMA INDEX

For the investigation of the relation between the condition of the stroma and the end-result, a "stroma index" was created. This stroma index represents the evaluation of the histologic structure of the stroma considered from the point of view of its antiblastic nature. For this compilation the factors 15 to 20 of the malignogram (table 2) received values which were the reverse of those evaluated in the malignogram. A high stroma index was regarded as indicative of a good local resistance, while a low stroma index was considered as evidence of a weak antiblastic reaction. The average stroma index calculated for the seventeen cases with end-result 1 was 14.8, ranging from 11 to 21. The average stroma index for the remaining thirty-one cases with end-results 2, 3 and 4 was 12.6, ranging from 8 to 18. The total range of the stroma index is from 6 to 24. The result of this study shows definitely that the

condition of the stroma has a certain influence on the prognosis of a carcinoma. But it offers at the same time evidence of the restricted nature of this effect, as is apparent from the relatively small difference between the average values in the two groups. The qualities of the parenchyma in its relation to those of the stroma seem to be of by far more importance in regard to the prognosis.

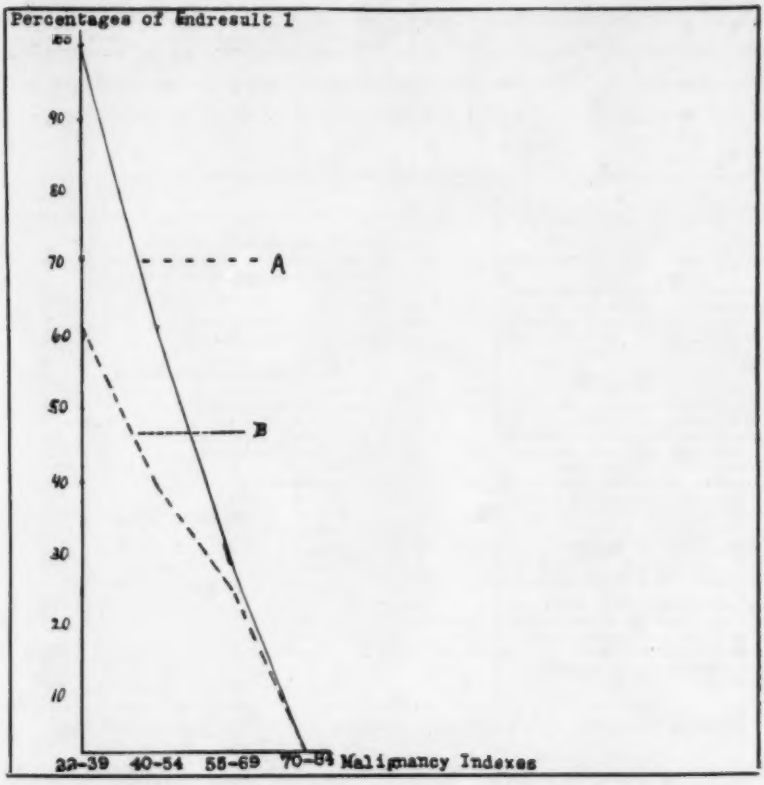

Chart 1.—Malignancy indexes to end-results. *A* indicates the malignancy line, and *B*, the old malignancy line (17).

END-RESULT AND PARENCHYMA-STROMA COEFFICIENT

For the purpose of substantiating this conclusion, the relation of the blastic properties of the parenchyma and the antiblastic qualities of the stroma to the end-result was studied. The blastic properties of the parenchyma were represented by the "parenchyma index," the sum of the evaluations of the factors 1 to 16 of the malignogram (table 2) which pertain to the parenchyma. The relation of the blastic properties of the parenchyma to the antiblastic qualities of the stroma was expressed by the value parenchyma index: stroma index or by the "parenchyma-

stroma coefficient." The parenchyma-stroma coefficients obtained in the forty-eight cases with known end-results were divided into two groups, those between 1 and 3.5 and those between 3.6 and 9. From chart 2 it may be seen that the parenchyma-stroma coefficient is apt to be low (1 to 3.5) in cases in which the prognosis is good or in which the disease runs a slow course, while in general it will be high (3.6 to 9) in cases in which the prognosis is relatively bad and the course rapid.

The average malignancy index in twenty-five cases that showed a large number of "pencil cells" was 51.6, corresponding to a mortality of 38.46 per cent. The average malignancy index in seven cases which showed a marked eosinophilic infiltration was 49.1, corresponding to a

TABLE 2.—*Histologic Malignogram* *

1. Special cell type of carcinoma.....	Spindle cell carcinoma, 75 per cent..... Round cell carcinoma, 15 per cent..... Spinous cell carcinoma, 10 per cent.....	8		
2. Nucleus-cytoplasm coefficient	10 per cent.....	1		
3. Irregularity in size of cells.....	Size 1 to 4.....	4		
4. Irregularity in shape of cells.....	Spindle, round, spinous, irregular.....	2		
5. Distinctness in outline of cells.....	More than 75 per cent distinct.....	1		
6. Chromatism of cytoplasm.....	Distinctly pink.....	1		
7. Functional activity of cells.....	In 15 per cent of cells keratin granules....	3		
8. Irregularity in size of nuclei.....	Size 1 to 4.....	4		
9. Irregularity in shape of nuclei.....	Spindle, oval, round, irregular.....	4		
10. Chromatism of nuclei.....	Somewhat paler.....	3		
11. Hyperchromatism of nuclei.....	Below 10 per cent.....	1		
12. Number of mitoses and prophases	Mitoses, 11; prophases, 5.....	3		
13. Irregularity of mitoses.....	Below 10 per cent.....	1		
14. Number of "pencil cells".....	In moderate number.....	2		
15. Infiltrative growth of cells.....	Well defined cell strands.....	1	4	
16. General type of carcinoma.....	Parenchyma, 75; stroma, 25 per cent.....	4	1	
17. Character of stroma.....	Moderately loose.....	3	2	
18. Vascularity of stroma.....	Very vascular.....	4	1	
19. Type of cellular infiltration.....	Lymphocytes.....	3	2	
20. Amount of cellular infiltration....	Slight.....	3	2	
Histologic malignancy index.....		56		
Carcinoma index (values numbers 1 to 16).....		43		
Stroma index (values numbers 15 to 20).....				12
Parenchyma-stroma coefficient (carcinoma index : stroma index).....		3.58		
Clinical group		2		
End-result		4		

* Frequent and large central necroses were found in the carcinomatous cell nests.

mortality of 38.46 per cent. In three cases showing marked eosinophilia and many pencil cells the average malignancy index was 41.67. These observations corroborate the statements of other workers in regard to the favorable prognostic significance of the eosinophilic infiltration and the presence of pencil cells. The latter cells were frequent in seven of seventeen cases with end-result 1 or in 41 per cent, while they were present in equal number in eight of thirty-one cases with end-results 2, 3 and 4 or in only 25 per cent. With this improved method I attempted an evaluation of the visible evidence of malignancy as present in the parenchyma of the tumor as well as of the antiblastic reaction of the body localized in the stroma. I am fully aware of the complicacy of my method, but believing that the prognosis and malignancy of a tumor do not depend on the value of one or a few factors but on a

multitude of factors of general and local nature and on their intimate interrelation, I had to take many factors into consideration to obtain reliable results. The malignancy index has as its object the evaluation of the potential malignancy of a tumor, that is, the sum of its proliferative, infiltrative, destructive and metabolic qualities, and an estimation of

Endresults	1	2	3	4	Number of Cases
1-3,5	15	6	4	1	26
3,6-9	3	4	5	10	22

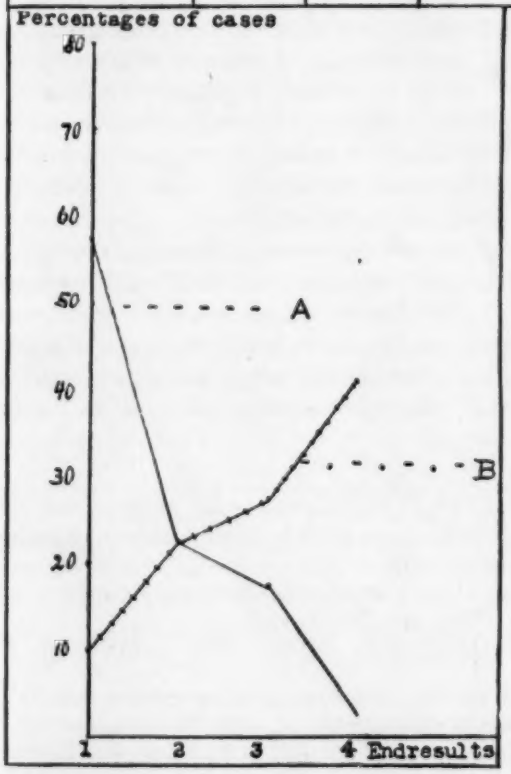

Chart 2.—Parenchyma-stroma coefficient. *A* indicates the parenchyma-stroma coefficient 1:3.5, and *B*, the parenchyma-stroma coefficient, 3.6:9. The curve shows that with increasing anaplasia and decreasing differentiation the antiblastic properties of the stroma do not increase correspondingly.

the local antiblastic forces present in the stroma. These two factors, together with the local blastic and general blastic and antiblastic qualities of the body, decide the prognosis of a tumor. Strong antiblastic proper-

ties of the body may temporarily prevent the free and unhampered activity of the tumor cells and may produce a latency of the malignancy of a tumor. Such a condition seems to exist in the preinfiltrative stage as described by Schiller [28] and to a certain degree still in the premetastatic stage as noted by Sticker [56] and Borst [2] on the basis of endogenous factors. It can be artificially produced by roentgen-ray and radium treatment, which causes a transitory change of the type of the tumor which appears to be more differentiated and less anaplastic (Levin and Joseph,[57] Alter,[45] Prym,[58] Hamperl and Schwarz [59]). On the other hand, the resistance against the tumor may be abnormally low, enabling the tumor cells to spread rapidly and to form early metastases (Derischanoff [60]). Wintz,[61] for instance, reported that about 15 per cent of all carcinomas produce early metastases at a time when the primary tumor is still relatively small, a circumstance to which he attributes the fact that 100 per cent cures will not be obtained with the present means of treatment. While in such cases a primary lack of body resistance is apparent, a sudden breakdown of this important factor may sometimes be observed as the result of inadequate treatment. It is well known that after operations for removal of a carcinoma which were accompanied by heavy loss of blood, marked shock and extensive traumatism of the tissue or after too intensive treatment with roentgen rays a rapid proliferation of tumor cells which remained behind is seen (Rosselet,[62] Anschütz [63] Jüngling,[64] Hohlfelder,[65] Raamsdonk [65]). After such impairment of the antiblastic qualities of the body, the tumor cells which enter the lymphatics and blood vessels and lodge in distant organs will not become any more actively destroyed, as observed by M. B. Fischer [3]

56. Sticker, quoted by Tyzzer (footnote 50).

57. Levin and Joseph: Morphologic Appearance of Cancer Clinically Cured by Radium and Roentgen Rays, J. A. M. A. **69**:1068 (Sept. 29) 1917.

58. Prym: Histologische Veränderungen nach Roentgenbestrahlungen beim Karzinom, Strahlentherapie **21**:319, 1926.

59. Hamperl and Schwarz: Zur genaueren Kenntnis der Roentgenwirkung auf Krebsgeschwülste, Strahlentherapie **24**:606, 1927.

60. Derischanoff: Die Kleincarcinome, Virchows Arch. f. path. Anat. **261**: 384, 1926.

61. Wintz: Erfahrungen mit der Beeinflussung innsersekretorischer Drüsen durch Roentgenstrahlen, Strahlentherapie **25**:105, 1927; Erfahrungen mit der Roentgenbehandlung des Karzinoms, ibid. **21**:368, 1926; Klinik der Bösartigen Geschwülste (Zweifel-Payr), 1927, vol. 3.

62. Rosselet: Ueber die indirekte Wirkung bei der Strahlentherapie, Strahlentherapie **25**:670, 1927.

63. Anschütz, quoted by Jüngling: Postoperative Irradiation of Carcinomas of the Breast, Beitr. z. klin. Chir. **139**:25, 1927; Foreign Letter, J. A. M. A. **89**:633 (Aug. 20) 1927.

64. Jüngling: Ist die prophylaktische Nachbestrahlung beim Mammakarzinon berechtigt? Strahlentherapie **22**:653, 1926.

65. Quoted by Jüngling (footnote 64).

in the capillaries of the lung, but they will stay alive and form metastases (Wood [66]). A weakening of the local resistance may also sometimes be effected by insufficient extirpation or radiation or other improper manipulations of the tumor. After insufficient roentgen-ray treatment, a temporary arrest of the tumor growth is first observed; this is followed by a more rapid proliferation of the tumor than that before the treatment. Tumor cells recover quicker from the effect of the roentgen rays than the normal cells (Wintz [61]). Moreover, the vitally strongest tumor cells stay alive, as is evident from the increase of the degree of anaplasia in the tumor tissue which has survived the therapeutic procedure (Hansemann [1]).

The existence of a self-control in carcinoma as assumed by Broders [12] seems rather remote to me and lacks any satisfactory foundation. Evidence does not exist that cancer cells change purposely from vitally active cells into vitally inactive cells unable to propagate further. If such a transition is observed, it is certainly not the result of an action of the cancer cell implying purpose and intention but a process manifesting an accidental quality of the tumor cell. The vital activity of these cells is controlled, as Plaut [6] has already emphasized, not only by intracellular factors but also by extracellular, local as well as general, ones. There is no cell in the body for which the quality of self-control could be claimed. They are all more or less the products of their environment. Cancer cells cannot be an exception to this rule in spite of the fact that they may possess a higher degree of independence than normal cells.

Any attempt at a predetermination of the course of a malignant tumor in which only a limited number of factors is considered, which, moreover, pertain exclusively to the appearance and structure of the tumor cells and the surrounding stroma, will remain defective as long as this procedure is not supplemented by an evaluation of factors through which the general status of the body against the malignant growth is more correctly determined than is possible with the present knowledge. A "clinical maligancy index" supplementing the "histologic malignancy index" would considerably improve the method that aims at the determination of the prognosis of malignant tumors.

In recent times there has been a steady increase in the number of investigators who believe that a carcinoma is not a purely local disease but that it is more or less the local manifestation of a disturbance involving the whole body, occurring at the point of least resistance or greatest exposure to the action of the causative factors (Opitz,[67] Teutsch-

66. Wood: The Clinical Value of Certain Phases of Cancer Research, Surg. Gynec. Obst. **44**:201, 1927.

67. Opitz: Ueber Krebs und Krebsheilung, Ztschr. f. Krebsforsch. **20**:108, 1925; Die biologischen Grundlagen der Strahlenbehandlung des Karzinoms insbesondere derjenigen des Uterus, Strahlentherapie **21**:353, 1926; Beiträge zu Problem der Gynäkologie und des Karzinoms, Berlin, C. F. Pilger & Company, 1925.

länder,[68] Elsner,[69] Askanazy,[70] Waterman [71] Weinzierl [72] and Greil [29]). These factors may be inherited or acquired, permanent or transient, local or general, exogenous or endogenous and varying in intensity in different organs. According to Teutschländer, the factors responsible for the genesis of a carcinoma can be divided into four groups: (1) general disposition; (2) local disposition on an endogenous or exogenous basis; (3) duration, quantity and character of the stimulus, and (4) specific factor of unknown nature. Opitz also assumed the existence of a factor of general character necessary for the formation of a tumor and stated that a treatment which does not remove this general disposition will never accomplish 100 per cent cures. He said, therefore, that therapeutic procedures employed in the treatment of persons with carcinomas have to exert an effect not only on the restricted area of the tumor but also on the body as a whole if they are expected to be successful. A similar opinion was held by Waterman.

FACTORS INFLUENCING MALIGNANCY

The present knowledge about the exact nature and significance of these factors of local and general character which contribute to the genesis and course of a malignant tumor is scanty and incomplete (Matzen,[73] Kraft [74]). The following list and discussion of factors of which a certain amount of information is possessesd may help to illustrate the complexity of this matter: age, sex, race, heredity, occupation, environment, living habits, previous infectious diseases, constitutional diseases, endocrine disturbances, alterations of the vegetative nervous system and reticulo-endothelial system, disturbances of the physical, chemical and fermentative status and metabolism of the tumor cells and of the whole organism.

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68. Teutschländer: Infektion und Krebs, Ztschr. f. Krebsforsch. **24**:223, 1927. Teutschländer and Schuster: Zur Histopathologie des experimentellen Teerkrebses, Ztschr. f. Krebsforsch. **23**:183, 1926.

69. Elsner: Tumorwachstum und endokrines System, Ztschr. f. Krebsforsch. **23**:28, 1926; Krebsentstehung und endokrines System, Berlin, S. Karger, 1926, pp. 100.

70. Askanazy: Ueber den Einfluss des Arsens auf verpflanztes embryonales Gewebe, Verhandl. d. deutsch. path. Gesellsch. **21**:182, 1926.

71. Waterman: Der heutige Stand der Chemotherapeutischen Carcinomforschung, Berlin, Julius Springer, 1926, pp. 74; Physikalisch-chemische Untersuchungen über das Karzinom, Biochem. Ztschr. **133**:535, 1922.

72. Weinzierl: Zur Frage der Wachstumsgeschwindigkeit der Carcinoma colli uteri, Monatschr. f. Geburtsh. u. Gynäk. **74**:322, 1926.

73. Matzen: Krebsstatistik in Bayern (1923) und die Verwertung der Ergebnisse zur Frage der Entstehung der Krebse, Ztschr. f. Krebsforsch. **25**: 105, 1927.

74. Kraft: Zur Carcinomfrage in Tyrol, Arch. f. klin. Chir. **134**:780, 1925.

Age.—It is a well established clinical experience that carcinomas in persons of less than 30 years of age are more malignant than those arising after this period (Ewing,[17] Plaut,[6] Fowler [75]). According to Fowler, cervical carcinomas in patients under 26 show a low degree of differentiation of the parenchyma and a lack of hyalinization, fibrosis and lymphocytic infiltration of the stroma. Kraul [76] reported a slower course of uterine carcinomas in old people which, according to his observations, is due to a predominance of mature carcinomas at this period of life. Weibel [77] noted that the percentages of cures decrease after the thirtieth year with increasing age. A tendency to lowered malignancy in the higher ages was stated by Boas [78] and Bergmann.[79]

Sex.—The variations in frequency of carcinomas of the same organ between the two sexes are well known. Ninety-eight per cent of carcinomas of the breast, for instance, occur in females and 2 per cent in males (Ewing [17]); 32 per cent of carcinomas of the stomach were found in females and 68 per cent in males (Kaufmann,[80] Bergmann [79]). Apparently there exists an inherited disposition or resistance of certain organs to carcinoma in the two sexes.

Race.—Similar conditions seem to be present in regard to the races. Pearl and Bacon [81] reported recently that carcinoma is more frequent among the members of the white race than among those of the colored races who live in the United States. Pittard [82] found that northern France, with a Nordic type of inhabitant, has a higher mortality from carcinoma than the southern part, with an Alpine and Mediterranean type of population. A similar observation was made by Deelman [83] in regard to the cancer mortality in northern Italy and southern Italy with their racially differing population. The marked discrepancy in frequency of carcinomas of the breast in England and the Netherlands may also be mentioned here (Deelman and Jitta [84]).

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75. Fowler: Malignant Epithelial Neoplasms, Carcinoma and Epithelioma, Occurring in Persons Under 26 Years of Age, Surg. Gynec. Obst. **43**:73, 1926.

76. Kraul, quoted by Plaut.

77. Weibel: 25 Jahre Wertheim'scher Karzinomoperation, Wien. klin. Wchnschr. **75**:1656, 1925.

78. Boas, quoted by Bergmann.

79. Bergmann: Handbuch der Inneren Medizin, Mohr-Staehelin, ed. 2, 1926, vol. 3.

80. Kaufmann: Spezielle Pathologische Anatomie, ed. 7, 1922, vol. 1.

81. Pearl, Raymond, and Bacon, A. L.: Biometrical Studies in Pathology, Arch. Path. **3**:963 (June) 1927.

82. Pittard, quoted by Deelman.

83. Deelman: The Mortality from Cancer Among People of Different Races, Surg. Gynec. Obst. **44**:247, 1927.

84. Deelman and Jitta: Die Sterblichkeit an Brustdrüsen-und Gebärmutterkrebs in Niederland und England, Ztschr. f. Krebsforsch. **24**:146, 1926.

Heredity.—Doubtlessly heredity represents another factor which may influence the origin and the course of cancer. Maud Slye,[85] in her well known experiments with mice, could show not only that a general disposition to carcinoma is inheritable but that even a disposition concentrated on a certain organ can be inherited. Discussion is still going on about the existence and significance of this factor in regard to carcinoma in man. But I do not believe that one can justly deny its existence without claiming special laws of heredity for the human race. The significance of this factor in the single case is still a matter of speculation on account of the lack of information about the diseases of our antecedents. However, it would be incorrect and misleading to claim the existence of a hereditary factor in the genesis of carcinomas in all those persons whose history records the occurrence of a malignant tumor in a member of their family. The possibility that purely exogenous factors may cause a malignant growth has to be taken into consideration. The presence of a hereditary factor was noted in carcinoma of the stomach in from 10 to 15 per cent by Bergmann;[79] in 5 per cent by Pauchet[86] and in 6.16 per cent by Anschütz.[63] Hereditability of cancer of the breast was observed in 13 per cent by Delbet[87] in 15 per cent by Snoud[88] and in from 5 to 10 per cent by Ewing.[17]

Malformations.—The origin of carcinomas from embryonally misplaced epithelial cells is generally recognized. These cells, detached from their normal connections and living under conditions which are for them more or less pathologic, represent elements which possess a tendency to undergo malignant changes more readily than normal cells. Nevi, pseudo-erosions of the cervix, misplaced cylindric epithelium in the esophagus and squamous epithelium in the stomach and endometrium, dermoids, enterocystomas, hypernephromas, etc., may be mentioned in this connection.

Endocrine Glands.—The endocrine glands which, according to Hart,[89] exert a regulatory function on the constitution and metabolism of the

85. Slye, Maud: Biological Evidence for the Inheritability of Cancer in Man, J. Cancer Research **7**:107, 1922; The Fundamental Harmonies and the Fundamental Differences Between Spontaneous Neoplasms and All Experimentally Produced Tumors, ibid. **8**:240, 1924; Discussion, Cancer Control, Surg. Gynec. Obst. **44**:102, 1927. Quoted by Maisin: The Anti-Cancer Campaign in Belgium, Surg. Gynec. Obst. **44**:68, 1927.

86. Pauchet: The Hereditary Transmission of Cancer, Foreign Letters, J. A. M. A. **89**:633 (Aug. 20) 1927.

87. Delbet and Mendaro: Les cancers du sein, Paris, Masson et Cie, 1921, p. 7; Épithéliomes mammaires sécrétants, Presse méd. **33**:553, 1925.

88. Snoud: Foreign Letters, J. A. M. A. **89**:633 (Aug. 20) 1927.

89. Hart: Konstitution und endokrines System, Ztschr. f. ang. Anat. **6**:71, 1920; Konstitution und Disposition, Berl. klin. Wchnschr. **55**:873, 1918; Ueber die Beziehungen zwischen endokrinem System und Konstitution, Berl. klin. Wchnschr. **54**:1077, 1917; Thymusstudien, Virchows Arch. f. path. Anat. **224**: 72, 1917.

body apparently have a certain influence on malignant tumors in genetic and developmental respects, as is evident from a large number of investigations. Döderlein [90] assumed the existence of "blastines" which he believed to be hormonal substances stimulating the proliferation of tumors and originating from endocrine glands. Fraenkel [91] and Régaud [14] recommended, probably from a similar consideration, a radiation of endocrine glands in addition to the ordinary treatment of carcinomas. Mühlmann [92] asserted that the endocrine glands influence the tumor through their effect on the vegetative nervous system. Clinical experience points to the fact that the endocrine disturbances present in diabetes mellitus and exophthalmic goiter represent antiblastic conditions because carcinomas are rarely observed in persons suffering from these diseases (Opitz,[67] Elsner,[69] Warburg,[93] Fischera [94]). Silberstein, Freud and Revecz [95] reported that the tolerance for insulin is increased in persons with carcinoma. Carcinomas are especially frequent in countries in which degenerations of the thyroid gland are often seen (Elsner [69]). The atrophy of the thymus and the decrease in function of the thyroid gland mark the beginning of the cancer age (Elsner [70]). Elsner stated further that persons with a persistent thymus have a higher carcinolytic titer of the blood than normal ones. Kaminer [96] observed that thymus extract has carcinolytic qualities. Teilhaber [52] saw some improvement in the condition of patients with carcinoma after implantation of spleen and thymus of calves or rabbits. Steindl [97] reported temporary arrest of tumor growth after the ligation of the spermatic duct. Coinciding with the atrophy of the sexual glands, a proliferation and new formation of nevi, papillomas, warts, etc., is frequently seen. These growths do not infrequently act as a basis of a subsequent malignant neoplasm. Loeb and

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90. Döderlein: Der Teerkrebs der weisen Maus, Ztschr. f. Krebsforsch. **23**: 241, 1926.

91. Quoted by Elsner.

92. Mühlmann: Wachstumsfermente, Virchows Arch. f. path. Anat. **230**: 384, 1926; Enzym als Geschwulstvirus, Ztschr. f. Krebsforsch. **22**:384, 1926.

93. Warburg: Neuere Arbeiten über Carcinom, Strahlentherapie **23**:1, 1926; Ueber der heutigen Stand des Carcinomproblems, Naturwissenschaften **15**:1, 1927.

94. Fischera: Beiträge zu Problemen der Gynäkologie und des Karzinoms, Berlin, C. F. Pilger & Company, 1925.

95. Silberstein, Freud and Revecz: Blutzuckerspiegel und Carcinom, Klin. Wchnschr. **4**:2252, 1925; Versuche inoperable Carcinome mit Insulin zu behandeln, Ztschr. f. d. ges. exper. Med. **55**:78, 1927.

96. Kaminer, Gisa: Die Biochemie des Karzinoms, Berlin, Julius Springer, 1926, pp. 52. Freund and Kaminer: Biologische Grundlagen der Disposition für Karzinom, Berlin, Julius Springer, 1925.

97. Steindl: Erfahrungen mit der Resektion des Vas deferens, Arch. f. klin. Chir. **130**:117, 1924.

Maud Slye [98] reported that the removal of the ovaries in mice before the onset of puberty renders these animals refractory to the development of spontaneous tumors but does not protect them against the tumor producing effect of tar. Maisin [99] noted that ovariectomy makes mice resistant to implantation of tumors, while it does not prevent the development of tar carcinomas. Peranchia [100] asserted that irradiation of the ovary arrests the production of an ovarian hormone, stimulating cellular proliferation and simultaneously increasing the antiblastic action of the spleen. Bateson [91] proposed and performed ovariectomy as a therapeutic procedure in the treatment of persons with mammary carcinoma. Definite information is not available in regard to the significance of the endocrine disturbance that exists during the time of pregnancy on the growth of malignant tumors. Carcinomas of the breast sometimes take a rapid course during this period (mastitis carcinomatosa acuta), while the progress of a carcinoma of the cervix uteri may be temporarily arrested (Ewing,[17] Katz). Von Borza and Melly [101] concluded from their experiments with mice painted with tar and fed with epinephrine, testiculin and thyroidin that these endocrine products effected the occurrence of carcinomas at an earlier date and of tumors of a more malignant type than those of the control animals. After irradiation of the hypophysis, Hofbauer [102] saw an increase of the eosinophilic cells in the blood, the significance of which I have already discussed, and of the choline content of the blood. Moreover, he subsequently observed degenerations appearing in the tumor and hyperemia, fibrosis and lymphocytic infiltration of the stroma. Opitz [67] reported favorable results from injections of a mixture of epinephrine and choline, substances that are partly antagonists. Mühlmann [92] stated that hypophysin has an effect favoring the growth of carcinomas.

Vegetative Nervous System.—The influence of the tonus of the sympathetic and parasympathetic nervous system on the functional activity of the organs of the body is generally recognized. The vital significance of this nervous system is emphasized by its close relationship to the endocrine system and the mineral metabolism. Considering

98. Loeb: Quantitative Relations Between the Factors Causing Cancer and the Rapidity and Frequency of the Resulting Cancerous Transformation, J. Cancer Research **8**:274, 1924; The Individuality Differential and the Result Against Transplanted Tissues and Tumors with Particular Reference to the Lymphocytic Reaction, ibid. **10**:252, 1926.

99. Maisin: Anticancer Campaign in Belgium, Surg. Gynec. Obst. **44**:68, 1927.

100. Peranchia: l'Aktinoter **5**:139, 1926.

101. Von Borza and Melly: Experimentelle Untersuchungen über das Wesen der Krebsdisposition, Virchows Arch. f. path. Anat. **262**:275, 1926.

102. Hofbauer: Klinische Beobachtungen bei Hypophysenbestrahlungen, insbesondere am Carcinom, Arch. f. Gynäk. **120**:194, 1923.

these facts, numerous workers investigated the relations between carcinoma, the vegetative nervous system and the effect of therapeutic management on both factors. Opitz [67] reported that persons with carcinoma usually have an increased sympathicotonus and less frequently show symptoms of a predominating vagotonus. After extirpation of sympathetic ganglions of the neck, Heim [103] saw degenerations occurring in a carcinoma of the cheek. Furthermore, he was unable to produce a carcinoma of the ear in rabbits by painting with tar after the resection of the sympathetic nerve of the ear. Ellinger [104] stated that choline administered to patients with carcinoma for therapeutic purposes acts through its effect on the parasympathetic system. Opitz,[67] von Pannewitz [105] and Risse [106] emphasized the fact that roentgen-ray treatment produces a stimulation of the vagus nerve.

Mineral and Lipoid Metabolism.—The direct interdependence between hormonal regulation, tonus of the vegetative nervous system and mineral metabolism is not yet definitely established. But there are numerous observations by which the existence of such a relation is made probable. Hoff [107] and Kraus and Zondek [108] asserted that the stimulation of the sympathetic nerve is equivalent to an increased dissociation of the H ions or is representing a calcium effect, while the stimulation of the parasympathetic nerve produces an increased dissociation of the OH ions and is equivalent to a potassium effect. Dresel [109] reported that a stimulation of the vagus nerve causes an alkalinization of the tissue (little colloidal calcium and much colloidal potassium) and of the blood (little ionized calcium, much total calcium, little potassium), while an increased sympathicotonus results in an acidification of the tissue (much colloidal calcium and little potassium) and of the blood (much iodized calcium, little total calcium and much potassium). McDonald,[110] in his

103. Heim: Sympathikus und Gewebsstoffwechsel, Deutsche med. Wchnschr. **52**:1856, 1926.

104. Ellinger, quoted by Eymer: Sollen die Gebärmutterkrebse operiert oder bestrahlt werden, Strahlentherapie **24**:149, 1926.

105. Von Pannewitz: Beiträge zur Pathologie des Säure-Basenhaushaltes, Arch. f. klin. Chir. **143**:697, 1926.

106. Risse and Poos: Roentgenbestrahlung und innere Sekretion, Klin. Wchnschr. **4**:323, 1925.

107. Hoff: Untersuchungen über das weisse Blutbild und seine biologischen Schwankungen, Krankheitsforschung. **4**:89, 1927.

108. Kraus and Zondek: Ueber die Durchtränkungsspannung, Klin. Wchnschr. **1**:1773, 1922. Zondek: Die Bedeutung des Antagonismus von Kalium und Calcium für die Physiologie und Pathologie, ibid. **2**:382, 1923; Hormonwirkung und Kationen, ibid. **2**:1344, 1923.

109. Dresel: Zum Blutchemismus der pharmakologischen Vagusreizung, Klin. Wchnschr. **4**:1066, 1925; Die Rolle de Lipoide im vegetativen System, ibid. **4**:816, 1925.

110. McDonald: Theory of Cancer Causation, M. J. & Rec. **125**:789, 1927.

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99. Maisin: Anticancer Campaign in Belgium, Surg. Gynec. Obst. **44**:68, 1927.

100. Peranchia: l'Aktinoter **5**:139, 1926.

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110. McDonald: Theory of Cancer Causation, M. J. & Rec. **125**:789, 1927.

theoretical considerations about the causes of carcinomatous growth, claimed that the increase of potassium and sodium over calcium and magnesium produces such an alkalinity, ionic association and increased permeability of all membranes that a state favoring cell division results. He believed that the therapeutic effect of roentgen rays lies in the promotion of an increased H ion concentration of the blood serum and a stimulation of the ionization of the bivalent elements, especially calcium. Opitz [67] stated that the H ion concentration of the blood of patients with carcinoma is increased and that therefore acidosis exists, while Kolta and Förster [111] asserted that the blood of these patients is more alkaline than that of normal ones. Moraczewski and Moor, however, found increased alkalinity of the blood in beginning carcinoma and acidosis of the blood in more advanced cases. Kulikov [112] reported that the tissue surrounding carcinomatous tissue is more alkaline than normal tissue, and he noted, furthermore, that a carcinoma may produce an uncompensated alkalosis. Lahm [25] observed that the nucleus of carcinoma cells was densely covered with calcium salts while the cytoplasm possessed a more scanty amount of these salts. Beebe,[113] Robin,[114] Rhodenburg and Krehbiel,[115] Clewes and Friebie,[116] Wolf [117] and others studying this subject came to the conclusion that in slowly growing tumors calcium is increased to twenty times the normal amount, but it is decreased in fast growing neoplasms in which potassium is increased. Calcium inhibits growth by thickening of the cytoplasm resulting in decreased vitality and proliferative activity, according to investigations of Muhlmann.[92] Potassium accelerates growth by thinning of the cytoplasm caused by an increased permeability of the cellular membrane which effects an increased vitality and proliferability. Waterman, experimenting with tar carcinomas, found the calcium in the stroma to be decreased and the potassium in the parenchyma to be increased. These changes in the mineral content of the carcinomatous tissue account for its increased electric conductivity (Lewis,[31] McDonald [110]). Beutner [118] stated that the

111. Kolta and Förster: Die Wirkung der Roentgenstrahlen auf das Blut, Strahlentherapie **21**:644, 1926.

112. Kulikov: Ionenkompensation im Organismus bei Entzündung und Krebs, Mosk. med. zurmal. **6**:18, 1926; abstr. in Ber. a. d. ges. Gynäk. u. Geburtsh. **12**:287, 1927.

113. Beebe: The Chemistry of Malignant Growths, Am. J. Physiol. **12**:167, 1904; **13**:341, 1905.

114. Robin: Compt. rend. Acad. d. Sc., 1913, vol. 156, p. 334, and 1919, vol. 168, p. 171.

115. Rhodenburg and Krehbiel: Studies of Mineral Salts in Their Relation to Malignant Tumors, J. Cancer Research **8**:423, 1924.

116. Clewes and Friebie: On the Relationship Between the Rate of Growth, Age and Postassium and Calcium Content of Mouse Tumors (Adenocarcinoma Jensen), Am. J. Physiol. **14**:173, 1905.

117. Wolf: Compt. rend. Acad. d. Sc., 1923, vol. 176, p. 1932.

118. Beutner: Ueber die Ursache der Neoplasie, Ztschr. f. Krebsforsch. **24**: 99, 1926.

increased potassium content of the carcinoma cells favors cytolysis and recommended the therapeutic use of magnesium, copper and lead salts to antagonize the effect of potassium and lactic acid present in the cancer cells. The malignancy of a carcinoma increases with its content of potassium, according to statements of Beebe.[113] Opitz [67] saw a stimulation of growth of implanted tumors after feeding potassium salts, but an inhibition of growth after feeding calcium salts. McCollum [119] stated that in carcinomatous tissue the tumor cells contain more potassium and the connective tissue stroma more calcium, a condition which is just the reverse of that present in normal tissue. Lewis [81] noted that the blood calcium level in persons with precancerous lesions is low. Levy-Dorn and Burgheim,[120] Borst,[2] Corson-White [121] and others found the cholesterol content of the blood and the cancer cells increased in patients with carcinoma. A decrease of the blood cholesterol after roentgen-ray treatment was seen by Mattich and Buchwald.[122] The same alteration was observed after radical operations and after spontaneous regressions followed by a new rise of the blood cholesterol when recurrences developed (Levy-Dorn and Burgheim,[120] Luden [123]). The cholesterol content of the blood is increased in sympathicotonic conditions, which frequently are present in carcinomatous patients (Opitz,[67] Borst [2]). Cholesterol acts as a stimulus to proliferation, as shown by the experiments of Borst [2] with mice painted with tar and fed with excessive doses of cholesterol. The calcium-potassium and the cholesterol-lecithin ratios of the cell are highly important because they control the permeability of the cellular membrane. Waterman,[71] therefore, proposed to direct the therapeutic management of carcinomas in such a way that either the permeability of the cancer cells would be restored to normal or it would be so excessively increased that lysis of the cancer cells results. The phosphorus quotient of the blood is considerably increased in patients with carcinoma, according to Opitz,[67] and phosphatids surpass the stearines in young cancer cells, according to Benett,[124] Cramer,[125] Roffo [126] and Blair-Bell.[22] The disturbances of the carbohydrate metab-

119. McCollum, quoted by Waterman.

120. Levy-Dorn and Burgheim: Zum Einfluss der Röntgenbestrahlung auf den Cholesteringehalt des gesunden und kranken Körpers, Strahlentherapie **22:** 538, 1926.

121. Corson-White, quoted from Kilduffe, R.: The Clinical Interpretation of the Blood Chemistry, Philadelphia, Lea & Febiger, 1927.

122. Mattich and Buchwald: Effect of Radiation on Blood Cholesterol, J. Cancer Research **9:**86, 1927.

123. Luden: Blood Cholesterol: Its Interpretation and the Value of Its Determination in Cancer Research, Canad. M. A. J. **12:**147, 1922.

124. Benett: The Cholesterol Content of Cancers in Rats, Biochem. J. **17:** 13, 1914.

125. Cramer, quoted by Waterman.

126. Roffo: Bull. de l'Assoc. franç. pour l'étude du Cancer **14:**5, 1925.

olism of the cancer cells are well known from the experiments and investigations of Warburg,[93] Bierich [30] and others. In the interpretation of these observations, Warburg differed from Bierich in that he believed that the cancer cells produce such an excessive amount of lactic acid by fermentation of dextrose that only a part of it can be resynthesized into dextrose, while Bierich supported the point of view that the production of lactic acid is not excessive, but that the cancer cell has lost the quality of resynthesis of lactic acid into dextrose. A hastening of tumor growth was observed by Opitz [67] in experimental cancer after feeding dextrose, but simultaneously also he noticed an increased action of his special antiblastic substances. Improved results from roentgen-ray treatment after intravenous injection of 10 per cent dextrose solution were reported by Mayer.[127] The mechanism of this phenomenon remains dubious. The favorable effect of the dextrose solution may be due to an activation of the general vitality or due to a temporary stimulation of the mitotic processes in the tumor resulting in the presence of a larger number of highly sensitive tumor cells at the time of radiation. In consideration of many of the reported observations, Opitz [67] recommended a diet for patients with cancer which does not contain any sodium chloride, potassium salts, cholesterol and animal lard, but one which is rich in calcium salts, lecithin and vegetable oils.

Reticulo-Endothelial System.—The results of investigations in recent years point to the existence of alterations of the endothelial, especially of the reticulo-endothelial, system in patients with carcinoma. Rhoda Erdmann [128] concluded from her experiments with animals, the reticulo-endothelial cells of which were blocked by India ink, that metastases occur only after a previous damage to the reticulo-endothelial cells. Transplantation of carcinoma cells without any stroma was unsuccessful after her investigation. She regarded cancer as a metabolic disease of the connective tissue. Heim [103] mentioned that changes in the permeability of the endothelial cells are important for the growth of cancer cells. Haendel [129] asserted that the condition of the reticulo-endothelial system has a marked influence on the resistance of the body to tumor and is responsible for the variations of this factor in the different organs.

Blood.—The significance of the cellular elements of the blood in regard to prognosis of carcinomas has already been discussed. For therapeutic purposes in carcinomatous patients Teilhaber [52] recommended an artificial lymphocytosis by bleeding, diathermy or small doses of

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127. Mayer: Künstliche Steigerung des Roentgeneffektes bei Tumoren, Fortschr. a. d. Geb. d. Röntgenstrahlen. **34**:546, 1926.

128. Erdmann, Rhoda: Carcinomstudien, Ztschr. f. Krebsforsch. **22**:83 (Dec.) 1924.

129. Haendel: Ueber die Beziehungen des Geschwulstwachstums zur Ernährung und zum Stoffwechsel, Ztschr. f. Krebsforsch. **21**:281 and 288, 1924; Krebszüchtung im Tier, Klin. Wchnschr. **6**:1535, 1927.

roentgen rays. Murphy and Morton [49] proposed the injection of unsaturated fatty acids to stimulate the lymphatic system to produce carcinolytic substances. Leukocytosis, lymphopenia and eosinophilopenia are regarded as prognostically unfavorable signs when present before and especially after roentgen-ray treatment (Kolta and Förster [111]). Sokoloff asserted that weakness of the lymphatic system creates a disposition to generalization of a carcinoma, and he warned, therefore, against the destruction of lymphatic organs by the improper use of roentgen-ray treatment. The infrequency of carcinomatous metastases in the spleen is well known. Recent investigations of Yokohota,[130] who found metastases in the spleen in 20 per cent of carcinomatous persons, seem to disprove this assumption, but it is evident that the metastases observed by Yokohota were in general microscopically small, did not show any remarkable proliferative tendencies and had not produced any reaction in the surrounding splenic tissue. The lymphocytosis so frequently present in exophthalmic goiter may also contribute to the antiblastic tendencies apparently existing in this disease. I may mention in this connection the recent investigations of Hoff.[107] This author asserted that the absolute and relative number of the cellular elements of the blood is to some extent dependent on the hormonal status of the body. He concluded from his investigations that a definite relation exists between the mineral metabolism, hormonal regulation, tonus of the vegetative nervous system and number of leukocytes. Sympathicotonus, acidosis and neutrophilic leukocytosis are correlated on the one hand and vagotonus, alkalosis and lymphocytosis on the other. Freund and Kaminer [131] reported the decrease of the carcinolytic qualities of the blood of patients with carcinoma. They claimed that the appearance of unsaturated fatty acids in the blood of these patients is responsible for this phenomenon. The carcinolytic titer of the blood increases after roentgen-ray treatment and decreases again when recurrences develop. The occurrence of physical changes in the blood of patients with carcinoma is demonstrated by the shortening of the sedimentation time of the erythrocytes (Giesecke,[132] Schmitz [16] and Guthmann and Schneider [133]) which may return to normal after roentgen-ray treatment. A renewed shortening of the sedimentation time may indicate a recurrence (Kappies [134]).

130. Yokohota: Ueber die mikroskopischen Krebsmetastasen in der Milz, Ztschr. f. Krebsforsch. **25**:32, 1927.

131. Freund and Kaminer (footnote 96, second reference).

132. Giesecke: Zentralbl. f. Gynäk. **45**:39, 1921.

133. Guthmann and Schneider: Die diagnostische und prognostische Bedeutung der Blutkörperchensenkungsgeschwindigkeit beim Carcinom, Arch. f. Gynäk. **127**:515, 1926.

134. Kappies: Blutkörperchensenkungsgeschwindigkeit und Heilerfolge beim Genitalkarzinom des Weibes, Klin. Wchnschr. **6**:1306, 1927.

Exogenous Factors.—There are numerous factors which produce changes in the organism as a whole or in part of it, acting as a basis for subsequent malignant neoplasms. They may create a purely acquired disposition or they may intensify an already existing inherited disposition.

(*a*) Infectious diseases, especially those of a chronic character, sometimes form such a basis. Chronic cervicitis, mastitis, gastritis, colitis, peridontitis, pancreatitis, hepatitis, chronic eczema of the skin (xeroderma pigmentosum, Paget's disease, Bowen's eczema), tuberculosis of the skin and bronchi, syphilitic leukoplakia of the tongue and chronic peptic ulcer are some of the diseases that may prepare the field for a subsequent neoplastic growth.

(*b*) Occupation is also a factor which in a certain percentage of cases is responsible for the development of a malignant tumor. The frequency of carcinomas among persons whose occupations bring them in contact with arsenic, aniline dyes, tar, paraffin, soot, roentgen rays, etc., is well known. Experimental evidence definitely supports the significance of these substances for the genesis of carcinomas.

(*c*) Habits of living that produce chronic irritations are also responsible in some cases for the production of a tumor. The carcinoma of the lip of smokers, the kangri cancer of the Indian natives, the carcinoma of the mouth of the Indian women due to chewing of betel nuts and the carcinoma of the esophagus of the Chinese and Bavarian peasants due to the drinking of strong alcoholic beverages are examples of this type of origin of carcinoma.

(*d*) Nutrition may also be a factor influencing the genesis and course of carcinomas. The vitamin theory of Burrows [135] is well known. He reported, furthermore, that carcinoma is prevalent in undernourished people, and Wintz [61] noted that the best results of treatment are obtained among members of the well to do class of people on account of their better nourishment. I may refer again to the dietary rules of Opitz.[67] Sugiura and Benedict [136] reported the dependency of growth and recurrences on the diet in carcinoma of mice.

(*e*) Environmental factors, such as climate, housing, soil, water supply, etc., may also exert an influence favoring the production of malignant neoplasms, eventually through their effect on the endocrine glands (Hart [89]). The existence of cancer houses, villages, valleys, etc., does not seem to me to be an absolute impossibility in spite of the lack of any conclusive evidence. Kraft reported that carcinomas of the stomach and of the esophagus are especially frequent in those parts of the Tyrol

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135. Burrows, M. T.; Jorstad, L. H., and Ernst, E. C.: Cancer, Vitamin Imbalance and Roentgen-Ray Activity, J. A. M. A. **87**:86 (July 10) 1926.

136. Sugiura and Benedict: Influence of Insufficient Diets Upon Tumor Recurrence and Growth in Rats and Mice, J. Cancer Research **10**:309, 1926.

that produce ichthyol. Pearce and van Allen [137] observed a decrease of malignancy in experimental carcinoma under constant light treatment.

Location also plays a rôle in the course of a malignant tumor. The specific structure of the organ involved, its blood and lymph supply and its specific resistance to tumor undoubtedly have an effect on the spreading of the tumor cells. Kokorin [138] stated that carcinomas of the breast, lung, bronchi, stomach, prostate gland, rectum, pancreas and kidney have a marked tendency to metastasize; those of the uterus, esophagus and maxilla have a moderate tendency, and those of the mouth, skin, larynx, urinary bladder, mandibula, nasopharynx and the female external genital organs, a low one.

The proliferative type of the tumor also represents a factor in regard to the prognosis of a tumor. It is a general clinical experience that exstructively growing tumors, such as the cauliflower carcinomas of the uterine cervix, are less malignant than the mainly infiltratively or destructively growing carcinomas of this organ.

This brief survey of a limited number of factors which may influence the genesis and the course of carcinomas in varying degrees may illustrate sufficiently the complexity of conditions with which the physician will have to deal in his attempt to treat successfully patients with carcinoma. Every one of these patients represents a problem of his own which has to be analyzed to its most minute details to enable the physician to make a reliable determination of the prognosis and institute a proper therapeutic management. It is obvious that only through close cooperation of representatives of various branches of medical science can such an analysis as outlined be made. If large series of patients accurately analyzed and remaining under direct medical supervision and care for a great length of time will be available for further study, the present knowledge about the nature and importance of the factors mentioned will be broadened, the existing discrepancies of opinion about the significance of the different factors will be removed and definite relations will be established between these factors which at present stand more or less isolated beside each other.

COMMENT

The accompanying histologic malignogram (table 2) in its present form represents an accurate numerical description of the histologic structure of the tissue examined. The clinician who can interpret the values recorded in this scheme receives a report which not only is complete but is so pregnant and impressive in its arrangement and expression that the

137. Pearce and Van Allen: Influence of Light on the Growth and Malignancy of a Transplantable Neoplasm of the Rabbit, J. Exper. Med. **40**:483, 1927.

138. Kokorin: Entfernte Metastasen der Krebsgeschwulste, Sammelh. d. chir. propaed. Klin. d. Inst. f. Geschwulstlehre d. I. Mosk. Staatsuniv. **3**:82, 1926.

salient points may be seen at a glance. The determination of the malignancy index will be best left to the pathologist. Such detailed and minute studies should not be attempted by any one who is not thoroughly familiar with the histology of malignant tumors or who is not willing or able to spend a sufficient amount of time on this painstaking investigation. As pathologic diagnoses in general should never be made at a glance, such a method is especially out of place in this kind of work. A malignogram with malignancy index can be accomplished in about twenty or twenty-five minutes after some experience with the method has been acquired. This time may be shortened to ten or fifteen minutes when the old method with its nine factors is employed. But it is obvious from this communication that any other attempt of simplification will impair the accurateness of the method. The technical details reported will enable any pathologist to duplicate my method. Through the introduction of well defined standards, my method of determination of histologic malignancy is freed, to a large extent, from the influence of personal experience and interpretation. The significance of the histologic malignancy index in regard to the prognosis is restricted through the existence of other factors of general and local nature which may exert an influence on the course of a carcinoma. This assumption is well illustrated by the occurrence of carcinomas in which the malignancy index does not correspond to the end-result obtained. Through a proper evaluation of these additional clinical factors, with due consideration of the existing therapeutic means, a valuable improvement of the method of determination of prognosis of malignant tumors may be accomplished in the future.

CONCLUSIONS

1. An attempt was made to determine the potential malignancy of carcinomas of the uterine cervix through an evaluation of twenty different histologic factors pertaining to the parenchyma and stroma of these tumors.

2. The evaluations are expressed in numerical values which represent an accurate numerical description of the histologic structure of the tissue examined.

3. The sum of the numerical values is called "histologic malignancy index."

4. The higher the malignancy index the worse is the prognosis, and the lower the malignancy index the better is prognosis.

5. The occurrence of carcinomas which do not obey this rule points to the existence of additional factors of local and general nature which exert an influence on the growth of carcinomas and which cannot be evaluated by a histologic method.

6. It is therefore proposed to supplement the "histologic malignancy index" by a "clinical malignancy index" in which these factors must be considered.

7. The method reported is freed to a large extent from the influence of personal experience and interpretation through the introduction of well defined standards, so that a duplication by other workers is made possible.

Notes and News

University News, Promotions, Resignations and Appointments.—Roger D. Baker and Arthur Koff have been appointed assistants in pathology in Johns Hopkins University.

At the University of Illinois, Eric A. Fennel has been appointed associate professor of pathology and M. Bohrod and M. I. Cohen have been appointed instructors in pathology.

P. Lecomte du Noüy, formerly associate member of the Rockefeller Institute, has been made a member of the Pasteur Institute of Paris. He has been put in charge of a new department of biophysics.

At the University of North Dakota, Charles B. McGlumphy has been appointed professor of pathology and bacteriology, and Jerome T. Syvertson, instructor in pathology and bacteriology.

At Baylor University, Dallas, Texas, Maurice L. Richardson, Western Reserve University, has been appointed professor of pathology in place of Rodger J. B. Hibbard, acting professor; Thomas B. Haslam, associate professor of pathology, and Harold E. Smith, assistant in pathology.

Arthur Weil, formerly neuropathologist at Montefiore Hospital, New York, has assumed the associate professorship of neuropathology in the institute of neurology of Northwestern University Medical School, Chicago.

William Charles White, Hygienic Laboratory, Washington, is now chairman of the division of medical sciences of the National Research Council.

J. A. Miller has been appointed professor of pathology in the University of Louisville, Ky., and has resigned as professor of clinical pathology in the University of Nebraska, Omaha, where he is succeeded by J. A. Weinberg.

In the University of Toronto, William L. Holman has been appointed professor of bacteriology and associate director of applied bacteriology, and William L. Robinson has been appointed associate professor of pathology.

Umberto Parodi, professor of pathologic anatomy in the University of Catania, Italy, has died, at the age of 49.

In the school of medicine of the University of Texas at Galveston, Paul Brindley has been made acting director of the department of pathology.

Edward L. Miloslavich has resigned as professor of pathology and director of the department of pathology and bacteriology in the school of medicine of Marquette University, Milwaukee.

Clarence Z. Garber, formerly of the department of pathology of the Ford Hospital in Detroit, is now associate in the department of pathology in Peking Union Medical College.

At the University of Chicago, William Robinson has been made assistant professor and Hilmeier Cohen instructor in the department of pathology under the Sprague Institute.

In the Harvard Medical School, Rubin Z. Schultz has been made instructor and Theodore L. Terry and John I. Bradley assistants in pathology. Lawrence Weld Smith, assistant professor of pathology, has resigned.

It is reported that the Nobel prize in medicine for 1928 has been awarded to Charles Nicolle, director of the Pasteur Institute of Tunis, for his work on typhus fever, especially on the rôle of lice in its transmission.

Robert A. Lambert has resigned as director of the School of Tropical Medicine of Columbia University in San Juan, Porto Rico, to become assistant director in the division of medical education of the Rockefeller Foundation.

Earl B. McKinley has been appointed professor of bacteriology in the College of Physicians and Surgeons, Columbia University, and director of the School of Tropical Medicine in Porto Rico.

Suit for Damage Alleging Necropsy Without Permission and with Mutilation of Body.—In September, 1927, a man was admitted to the hospital of the State University of Iowa, as suffering from thermic fever. The patient died within one hour after admission. The record at the hospital stated that the patient was divorced, and that his mother was the responsible relative. The mother was summoned to the hospital and, on request, gave her consent to a post-mortem examination, which was made the same day. The cavities of the trunk were filled with sawdust, the normal eyes were replaced with carefully matched artificial eyes and the cranial cavity filled with bandages of plaster of paris. In February, 1928, it was learned that a daughter of the patient, living in St. Louis, had ordered the body to be opened again before burial. Suit for damages, in the amount of $25,000, alleging mutilation of the body and lack of permission to make the necropsy, has now been brought against the physician who obtained the permission of the mother, against the physician who authorized the examination on the part of the administration of the hospital and against the pathologist of the hospital.

Registry of Thoracic Tumors.—The American Association for Thoracic Surgery has established a registry of thoracic tumors in order to stimulate the clinical and pathologic study of such tumors. The registry will include all primary intrathoracic tumors and all primary tumors of the chest wall and thoracic vertebrae that impinge on the pleural cavity. The registry is in charge of a committee of which Dr. George J. Heuer is chairman. All communications should be addressed to the registrar, Dr. William De W. Andrus, Cincinnati General Hospital.

Abstracts from Current Literature

Pathologic Physiology

THE EFFECT OF NICOTINE AND CAFFEINE ON THE GROWTH OF CHICKENS. R. E. CHASE, Am. J. Physiol. **85**:527, 1928.

While nicotine administered daily into the crops of growing chicks often produced transient symptoms of marked intoxication, it was found to have no deleterious effect on their growth. Caffeine, on the other hand, caused a marked retardation.

H. E. EGGERS.

THE EFFECT OF COLECTOMY ON THE INCIDENCE OF PARATHYROID TETANY AND THE BLOOD CALCIUM. E. OLDBERG and E. L. WALSH, Am. J. Physiol. **85**:531, 1928.

The writers find that in dogs, when colectomy precedes parathyroidectomy, there is a delay in the onset of tetany, and a modification of its course. Occasionally it entirely fails to appear. When the two operative procedures are reversed, there is at most a transitory depression of the tetany. In normal dogs colectomy causes a rise of blood calcium of from 1 to 3 mg. in the course of a week. They are inclined to base their observations on the theory that parathyroid tetany is essentially due to calcium deficiency.

H. E. EGGERS.

THE EFFECTS OF HISTAMINE, FORMALDEHYDE AND ANAPHYLAXIS UPON THE RESPONSES TO ELECTRICAL STIMULATION OF GUINEA-PIG INTESTINAL MUSCLE. G. H. BISHOP and A. I. KENDALL, Am. J. Physiol. **85**:546 and 561, 1928.

The response to electrical stimulation of intestinal muscle of the guinea-pig was studied when weak solutions of histamine or formaldehyde were applied to the serous surface of the gut strip. Increased response was noted with histamine; a diminished response with formaldehyde. In sensitized animals, the homologous protein was found to affect the muscular response as did the histamine. The circular musculature was found to be more sensitive to the chemical action, and less so to the electrical stimulation. When the mucosa of a segment of the gut of a guinea-pig was irrigated with oxygenated Tyrode's solution there was a loss of rhythmicity and a depressed response to electrical stimulation. This was especially the case with the circular musculature. A reversal of the phenomenon was observed when the irrigation was stopped. Histamine added in threshold doses to the irrigating fluid restored rhythmicity and response to electrical stimulation. Larger amounts caused shortening. Similar results followed the addition to the fluid of the homologous serum in the case of gut of sensitized animals. The addition of formaldehyde to the Tyrode bath outside the irrigated gut relaxed and depressed the muscle, whether this was under the influence of histamine or in a state of moderate anaphylactic contraction.

H. E. EGGERS.

THE EFFECT OF EXCESSIVE AMOUNTS OF WATER ON THE VOLUME AND COMPOSITION OF THE BILE. A. M. SNELL and L. G. ROWNTREE, Am. J. Physiol. **85**:577, 1928.

Water intoxication in dogs with permanent biliary fistulas was found to diminish the total output of bile and the elimination of biliary acids. The latter effect was much more pronounced than that on the output of bile and the elimination of bilirubin. The effect varied with the condition of the animal as regards both extent and duration. When half of the intoxicating dose of water was given, only minor

changes in biliary output were observed. The changes in bile flow incident to water intoxication are ascribed to waterlogging of the liver with depression of its function.

H. E. EGGERS.

THE TOXIC FACTOR IN BILE. O. H. HORRALL and A. J. CARLSON, Am. J. Physiol. **85**:591, 1928.

Bile removed from the gallbladder of dogs was administered to other dogs by several parenteral routes, and was found to be definitely toxic. The toxicity was not affected by bacterial contamination, by freezing or boiling, and the toxic factor was dialyzable. Bilirubin was found to be nontoxic. The same was true of pure bile acids, owing to their insolubility. The cholate portion of their salts — sodium glycocholate and taurocholate — was toxic.

H. E. EGGERS.

BASAL METABOLISM OF NORMAL PERSONS WITH CONSIDERATIONS OF PREDICTION STANDARDS. F. G. BENEDICT, Am. J. Physiol. **85**:607, 1928.

Benedict here reports a supplementary series of normal metabolism tests made on twenty-seven men and thirty-three women. In general, these were of higher ages than those studied previously, and included persons of unusual configuration. Average results of this series were lower — due in part to more truly basic conditions and in part to the fact that the data are as a rule the result of several days' determinations. With the men, the determinations averaged 1.8, 4.4 and 0.4 per cent less than the results predicted by the Harris-Benedict, the Aub and DuBois, and the Dreyer standard tests, respectively. For the women, the average respective variations were —4.2, —7.3 and —4 per cent. The widest divergences occurred in the case of subjects of unusual configuration. Benedict urges a more critical consideration of the prevailing methods of prediction, especially as regards persons of unusual configuration and those suffering from endocrine disturbance. Apparently the present prediction standards for women should be lowered by about 5 per cent but with care in the interpretation of those cases which this shift would throw outside the normal limit of 10 per cent variation.

H. E. EGGERS.

THE BASAL METABOLISM OF SOME BROWNS AND BLACKS IN JAMAICA. M. STEGGERDA and F. G. BENEDICT, Am. J. Physiol. **85**:621, 1928.

Basal metabolism, determined on thirty-seven browns in Jamaica, showed a heat production averaging 5.4 per cent lower than that predicted by the Harris-Benedict standard for the corresponding class of whites. With five brown women the metabolism averaged 3.4 per cent below the prediction for white women. Since the latter standard is admittedly too high, there would appear to be less disparity between brown and white women than in the case of men; but the number studied was too small to permit definite conclusions. With eight full blooded blacks, the average was only 2 per cent below the calculated standard — practically the same as for northern whites. The similarity in metabolic rates between brown and northern white women, and black and northern white men, would suggest that the tropical climate and diet of Jamaica did not have a pronounced effect on heat production.

H. E. EGGERS.

THE BASAL METABOLISM OF MAYAS IN YUCATAN. G. D. WILLIAMS and F. G. BENEDICT, Am. J. Physiol. **85**:634, 1928.

Advantage was taken of an archeologic expedition to Chichen Itza to make comparative studies of the basal metabolism of whites in different climatic circumstances, and of the indigenous Maya Indians. In the case of the whites, determinations made before, during and after a short stay in Yucatan, did not betray any differences in heat production. With thirty-two male Mayas the metabolic rate

averaged 5.2 per cent above that of white men of similar age, weight and height. It is believed that this difference is due to some inherent factor, probably racial. This observation, along with that of a lowered rate for Orientals, argues against the interpretation of a low metabolic rate as an indication of "racial inferiority," or a high rate as an indication of the reverse.

H. E. Eggers.

Age and Basal Metabolism of Adults. F. G. Benedict, Am. J. Physiol. **85**:650, 1928.

The basal metabolism of three men and one woman has been determined over a period of years, permitting the study of its variations in the same subject. The woman was studied from the age of 24 to 36 years, with almost no change during that period. The age range represented by the men was from 30 to 59 years, and in two a definite lowering of metabolic rate with increasing age was noted. In the third subject an increase of weight and a pronounced improvement in general physical condition masked changes that might otherwise have been present. The principal change in the two men occurred at the ages of 47 and 42 years. It is concluded that alteration of basal metabolism is an accurate index of increase or decrease of physical vigor.

H. E. Eggers.

Basal Metabolism Before and After a Summer Vacation. F. G. Benedict and M. D. Finn, Am. J. Physiol. **85**:665, 1928.

A study of the basal metabolism of twenty subjects before and after vacations of one month failed, as a rule, to show any appreciable change, even though there frequently was a marked improvement in subjective condition.

H. E. Eggers.

The Antagonism Between Insulin and Pituitary Extract. Helmuth Ulrich, Arch. Int. Med. **41**:875, 1928.

A case of acromegaly is reported, with glycosuria and hyperglycemia in which there was atypical response to insulin therapy, its effectiveness being much impaired. The observations in this case are reviewed especially with reference to the antagonistic effect of hyperactivity of the posterior pituitary lobe on insulin.

H. R. Fishback.

Acromegaly and Diabetes. W. M. Yates, Arch. Int. Med. **41**:883, 1928.

Diabetes is found to be present in acromegaly in an average of perhaps from 10 to 12 per cent of the cases. Disorders of the pituitary without acromegaly are not commonly accompanied by diabetes. Increased tolerance for carbohydrates is usual in hypopituitarism.

In a series of seventy-nine patients with acromegaly at the Mayo Clinic, glycosuria was observed in eight. Six cases studied more closely as to diabetes are reported. Acromegalic diabetes is demonstrated as being similar to ordinary diabetes mellitus. In three of the cases the condition was controlled by diet alone, while in the other three insulin was required. The response to insulin was just as striking as in any case of diabetes. In those cases complicated by hyperthyroidism, there was the usual increase in the basal metabolic rate. It has been suggested further that the basal metabolic rate may be increased by a substance produced by the anterior pituitary lobe.

The only difference between diabetes alone and acromegalic diabetes lies in the rare spontaneous temporary or permanent disappearance of the latter. It may be due, as ordinary diabetes, to an insufficient production of insulin, or enough insulin may be secreted but it is possibly neutralized by some new substance.

H. R. Fishback.

EXPERIMENTAL HYPOTENSION IN RABBITS. T. L. SQUIER and C. T. BACH, Arch. Int. Med. **42**:56, 1928.

Bacterial cultures were made from the apexes of extracted teeth, from tonsils and from prostatic secretions. The cultures were injected into the marrow cavity of the tibia, into the knee joint, or intravenously, in rabbits. A significant fall in blood pressure occurred in a large percentage of rabbits injected with cultures obtained from patients with systolic blood pressures below 110. Cultures from patients with normal blood pressures did not cause significant changes in the blood pressure in injected animals.

H. R. FISHBACK.

THE HEREDITARY FACTOR IN SOME DISEASES OF THE HAEMOPOIETIC SYSTEM. HUMPHREY ROLLESTON, Bull. Johns Hopkins Hosp. **43**:61, 1928.

This is a valuable summary of the literature on the rôle of heredity in various diseases of the hemopoietic system.

THE THRESHOLD FOR ELECTRICAL EXCITATION OF THE MOTOR CORTEX OF ANESTHETIZED MAMMALS. SARAH SHELDON TOWER, Bull. Johns Hopkins Hosp. **43**:237, 1928.

The threshold for electrical excitation has been determined for the motor cortex of anesthetized animals under constant conditions of anesthesia and body temperature and with routine experimental procedure. The value of this threshold was characteristic for each of the two species used, cat and dog. The effect on this threshold of varying the intracranial pressure by the intravenous injection of hypertonic and hypotonic solutions has been studied and found negligible. Moreover, the increase in brain volume resulting from the injection of hypotonic fluids had no measurable effect on the excitability of the motor cortex. The decrease in brain volume, following the injection of hypertonic solutions, was, on the contrary, accompanied by a proportionate raising of the threshold, or lowering of the excitability of the motor cortex. The reaction of lowest threshold obtained from the motor cortex was inhibition of extensor tone. The general significance of these results is considered, together with their relation to the precipitation of epileptic attacks and their control.

AUTHOR'S SUMMARY.

THE ETIOLOGICAL RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA. W. B. CASTLE and E. A. LOCKE, J. Clin. Investigation **6**:2, 1928.

The frequent marked reduction of gastric hydrochloric acid and pepsin in pernicious anemia is not benefited by general improvement of the patient. Since the effective principle of liver extract is probably polypeptid in nature, deficient gastric digestion of protein may play a part in causing the anemia.

The stomach contents of a normal man were recovered daily one hour after he had eaten rare hamburger steak, which also had been given to ten patients with pernicious anemia. In eight of these, clinical and blood improvement was obtained, similar to that found after small doses of liver in such patients.

Other mixtures were also tried, such as hamburger steak and pepsin, hamburger and hydrochloric acid, and hamburger steak alone. No benefit was obtained in any.

It is suggested that pernicious anemia may be caused by the failure of the achylia stomach to provide the substance which helps to maintain the blood in the normal person.

LIVER FRACTIONS IN PERNICIOUS ANEMIA. R. WEST and E. G. NICHOLS, J. Clin. Investigation **6**:3, 1928.

Previously the authors have proved the efficacy of a 60 per cent alcohol extract of liver in raising the blood count of patients with pernicious anemia.

The residue of this alcohol extract was dissolved in water and the solution saturated with ammonium sulphate. The precipitate was found to be inert, and the filtrate active.

Liver extract prepared according to the method of Cohn was treated with basic lead acetate, and further with phosphotungstic acid. The phosphotungstic acid precipitate was active. It was then fractionated by Kossel's silver method. The histidine and argenine fractions combined gave no response, while the lysine fraction was active in two cases of pernicious anemia.

Negative results were obtained with pure choline, with a mercuric sulphate precipitate of a 60 per cent alcohol extract of liver, and a probable negative with glutathione.

THE PRINCIPLES OF CAPILLARY BLOOD-PRESSURE MEASUREMENTS AS APPLIED TO GLOMERULAR AND TUBULAR FUNCTION IN THE KIDNEY. LEONARD HILL and JAMES M. MCQUEEN, Brit. J. Exper. Path. **9**:127, 1928.

There is no evidence of a pressure in the glomerular capillaries adequate for overcoming the osmotic pressure of the plasma colloids and producing filtration of fluid into the Malpighian capsules. The fluid in the capsules counterbalances the pressure in the glomerular capillaries, and only a small excess of pressure in the capillaries suffices to maintain the flow of blood. There is evidence that while blood flows as usual through glomerular capillaries in the resting kidney, no fluid passes into the capsules. The distention of the capsules with fluid is brought about by specific action of diuretics.

PEARL ZEEK.

THE CAPILLARY BLOOD-PRESSURE IN RELATION TO OEDEMA AND CEREBRAL AND INTRA-OCULAR PRESSURE. LEONARD HILL, Brit. J. Exper. Path. **9**:135, 1928.

The capillary pressure in the various organs of a frog is measured by the Roy and Graham-Brown apparatus, using the momentary stoppage of the flow as the index, or first sign, of a velocity pulse. Stoppage of flow in systole produces banking up of the pressure to that in the artery supplying the compressed part. More than half the pressure in this artery is spent in maintaining the velocity of flow in the arterioles and capillaries. The pressure in the capillaries is counterbalanced by that of the tissue fluids, and the excess of capillary pressure is insufficient to overcome the osmotic pressure of the plasma colloids and produce filtration of fluid. The passage of fluid in and out of the capillaries is controlled by changes in the endothelial membranes, blood and tissue cells.

PEARL ZEEK.

RESEARCHES IN LACTATION. MARGARET FRANCES LOWENFELD AND SIBYL TAITE WIDDOWS, J. Obst. & Gynec. Brit. Emp. **35**:114, 1928.

The development of lactation varies in different women in the rate of appearance and composition of the milk. Two types of development are distinguished. In one the breast shows some activity during the later weeks of pregnancy; the milk comes in early, is not viscid and the color is rarely deeper than a primrose; it is homogeneous, early obtainable in definite amounts, and the protein and ash contents are low. The calcium is not affected. This is found mainly among multipara. In the second type, the breast is inactive during pregnancy, does not produce an appreciable secretion until after the first twenty-four hours after delivery, is viscid, variable in color, not homogeneous, and is obtained in small quantities. The protein and ash contents are high. This type is more frequent in the primipara. The duration of colostrum depends on the type and development present, and on the vigor of sucking in the infant. Small quantities of early milk have food value approximating to larger quantities of mature milk. While the time the sample is taken and the method of extraction, vigorous or gentle, do not affect the percentage of calcium and ash, the percentage of fat is dependent inversely on the amount of fluid present in the breast at the time of extraction, and on the amount of pressure exerted on the areola. Morbid states of the breast appear to be correlated with disturbances in the sugar content of the milk.

A. J. KOBAK.

THE RÔLE OF THE LUNG IN THE INTERMEDIARY NITROGEN METABOLISM. A. TSCHARNY and S. KRASSOWITZKAJA, Beitr. z. Klin. d. Tuberk. **69**:373, 1928.

The collapse of a considerable part of pulmonary tissue causes an increase of the nonprotein nitrogen of from 30 to 70 mg. per hundred cubic centimeters of venous blood. In patients with pneumothorax, the increase of the nonprotein nitrogen is in direct proportion with the amount of compression. The nonprotein nitrogen content may increase from 100 to 200 per cent. These studies confirm the theory again that one function of the lung is retention of nitrogen: this function is independent of the respiratory function.

MAX PINNER.

SUPRARENAL GLAND IMPLANTATION IN ADDISON'S DISEASE. A. REINHART, München. med. Wchnschr. **75**:1027, 1928.

A patient with Addison's disease improved markedly after a homoplastic implantation of suprarenal gland tissue. The report was written six months after the transplant was made.

E. F. HIRSCH.

BASAL METABOLISM OF PREGNANCY AND THE PUERPERIUM. F. WESENER, München. med. Wchnschr. **75**:1285, 1928.

The basal metabolism at the end of pregnancy is increased, on the average of 10 per cent. During the puerperium (from six to sixteen days) a rapid lowering of the metabolism occurs, on the average of 3.2 per cent. There is a parallelism between the increased basal metabolism and the depth of respiration.

AUTHOR'S SUMMARY.

CONCERNING BLOOD REGENERATION. L. HOLLANDER and S. V. PELLATHY, Folia haemat. **36**:12, 1928.

The authors found that regular bleeding of the sheep does not change the regenerating power of the blood provided the amount of blood withdrawn does not exceed one twentieth of the entire amount of the animal's blood.

B. M. FRIED.

Pathologic Anatomy

CORPUS LUTEUM HEMATOMA. S. A. WOLFE, Am. J. Obst. & Gynec. **15**:513, 1928.

Wolfe designates as hematoma the condition in which more than half the central cavity of the corpus luteum is filled with blood. He confirms the observations of other investigators, namely, that rupture of the graafian follicle is not associated normally with bleeding into the central cavity. The hematomas were studied in three phases of development of the corpus luteum: vascularization, efflorescence and regression. Functioning hematomas with corresponding cyclic changes in the endometrium were noted in the first two phases of development. The majority of hematomas are found in the regressing corpus luteum because of the normal prolongation of this phase. The normal corpus luteum shows moderate bleeding into the cavity during vascularization. In general this appears as a narrow zone in the cavity, in contact with the lutein columns. Secondary bleeding occurs with beginning involution; hence, it is associated with menstruation. Recurrent bleeding into the regressing corpus luteum follows with each subsequent menstruation until the avascular corpus albicans is formed. Excessive bleeding or hematoma is associated with pathologic hyperemia of the ovaries.

A. J. KOBAK.

PEDUNCULATED CYSTIC ADENOMYOMA OF THE UTERUS, OCCLUDING THE VAGINA. E. SAYLOR, Am. J. Obst. & Gynec. **15**:650, 1928.

This report concerns a large, pedunculated, cystic adenomyoma attached to the wall of the uterine cavity above the internal os and occluding the vaginal canal in a middle-aged multipara. The current popular theories of the formation of this type of tumor are discussed.

A. J. KOBAK.

THE RETICULO-ENDOTHELIAL CELLS OF THE UTERUS: AN EXPERIMENTAL STUDY. C. F. FLUHMANN, Am. J. Obst. & Gynec. **15**:783, 1928.

The phagocytic cells in the uterus of rabbits were studied by Fluhmann by means of the intravenous injection of trypan blue or lithium carmine. The animals were studied in three groups. The first series, consisting of nonpregnant animals, disclosed macrophages in the vagina and uterus in only comparatively small numbers. The second series, studied after the introduction of 20 per cent silver nitrate into the upper part of the vagina had produced an aseptic inflammation, showed macrophages at the site of the lesion similar to those found in other connective tissues of the body. The response in the cornua, fallopian tube and lateral ligaments was also marked. In the last group, studied during gestation, an appreciable increase in the number of these cells persisted during puerperium.

A. J. KOBAK.

INFLAMMATION OF THE AMNION AND CHORION. R. S. SIDDALL, Am. J. Obst. & Gynec. **15**:828, 1928.

In a study of 1,000 cases, the placentas in 48 (4.8 per cent) showed inflammation of the fetal membrane. In 17 cases of intrapartum fever, the placentas in fifteen showed inflammation. Siddall believes that the presence of fever during labor, in the absence of any other determinable intercurrent infection, indicates intra-uterine infection. The abscence of fever, however, does not exclude the possibility of placental infection, since the placentas in 32 cases (70 per cent) showed inflammation of fetal membrane with bacteria demonstrated in two cases. Premature rupture of the bag of waters was an essential factor.

A. J. KOBAK.

MIXED TUMORS OF THE UTERINE CERVIX ("BOTRYOID SARCOMA"). D. M. COX and W. L. BENISCHEK, Am. J. Obst. & Gynec. **16**:28, 1928.

Mixed tumors of the cervix are rare. They are of mesodermal origin and are composed mainly of connective tissue. Two cases are reported. One, an infant, revealed the tumor as a grape-like cluster protruding through the vagina and attached to the cervix. In the other, an adult who had been pregnant for from two to three months, the growth at first was confused with hydatidiform mole; grape-like masses originated from the vaginal portion of the cervix, and biopsy confirmed the tentative diagnosis of botryoid sarcoma. Both patients died, and the growths were found to have spread by direct extension.

A. J. KOBAK.

DIFFUSE PELVIC ENDOMETRIOMA CONSTRICTING THE URETERS. A. MORSE and ISABELLA H. PERRY, Am. J. Obst. & Gynec. **16**:38, 1928.

The article describes a diffuse endometrioma involving all the pelvic structures associated with girdling and constricting of the ureters and secondary renal infection. The patient, white, aged 32, was observed for a period of five years. Painful menses which had begun three years prior to the time first seen, became progressively worse, with progressively painful and difficult urination during menstruation. Irregularly dilated glands were scattered through the mass surrounding and constricting the ureters. Some of these glands were surrounded by fibrous tissue and others by a varying quantity of loose stroma. Physiologic activity of this

misplaced endometrial tissue was indicated by the symptoms during menstruation, and by the presence of granular particles of brown pigment and shadows of red blood cells within some of the gland lumens.

A. J. KOBAK.

THE PATHOLOGIC AND CLINICAL SIGNIFICANCE OF CONGENITAL ONE-SIDED DEFECT OF THE KIDNEY, WITH THE PRESENTATION OF THREE NEW CASES OF AGENESIA AND ONE OF APLASIA. C. H. FORTUNÉ, Ann. Int. Med. **1**:377, 1927.

Fortune adds three cases of unilateral agenesia of the kidney to the 419 instances which he collected from the literature. The ureter on the affected side was said to be absent in 54 per cent of the cases and present in 10 per cent, while the absence of the renal vessels was noted in 100 cases. In forty-six cases, the suprarenal gland was reported absent. Associated genital malformations, usually due to arrested development of derivatives of the Müllerian or wolffian duct, occurred in 70 per cent of the female and 22 per cent of the male patients studied. A single existing kidney is more likely to become diseased than two normal kidneys. A case is reported of left renal aplasia, associated with the following multiple anomalies: cheilognathopalatoschisis, Meckel's diverticulum, multiple diverticula of the colon, malformations of the ear and stenosis of the aortic isthmus.

WALTER M. SIMPSON.

REGENERATION OF TUBULAR EPITHELIUM IN THE HUMAN KIDNEY FOLLOWING INJURY BY MERCURIC CHLORIDE. W. C. HUNTER, Ann. Int. Med. **1**:463, 1928.

Hunter takes issue with what he considers the general belief that renal epithelium has only a slight regenerative capacity. Reports are referred to of regeneration of renal parenchyma in animals following poisoning with chronic acid and uranium. In the case described by Hunter, a woman took a large quantity of mercuric chloride with suicidal intent. Epigastric pain, incessant vomiting of blood-tinged fluid, profuse diarrhea and stomatitis followed the ingestion. Anuria occurred during the first three days, followed by scant urinary excretion during the next ten days. Albuminuria was constantly present and tubular casts, erythrocytes and leukocytes appeared after the first few days. Death occurred on the fourteenth day. At the autopsy, the kidneys were found to have increased in size to 195 Gm. Microscopic examination revealed that the epithelium of the proximal convoluted tubules had been largely replaced by newly formed cells, differing in size, shape and staining qualities, and showing many mitotic figures. The distal, straight and collecting tubules and the glomeruli did not show any noteworthy alterations. Using mercuric chloride as the nephrotoxic agent, Hunter found similar regenerative changes in the kidneys of rabbits.

WALTER M. SIMPSON.

TUBERCULOSIS OF THE GALLBLADDER. J. T. CASE, Ann. Int. Med. **1**:482, 1928.

A case of primary tuberculous cholecystitis in which the involvement of the gallbladder is presumably primary is added to the ten already reported.

WALTER M. SIMPSON.

THE NATURE OF THE PRIMARY RENAL LESION PRODUCED BY LEAD. SLAVKO PEJIC', Ann. Int. Med. **1**:577, 1928.

Pejic' undertook to determine: (1) the appearance of early histologic lesions caused by lead carbonate in the kidneys of guinea-pigs; (2) the quantity of lead carbonate required to produce demonstrable lesions and (3) the length of time required for the appearance of these changes. Previous writers on the subject differ as to whether the renal changes in nephritis saturnina are primarily parenchymatous or vascular or both. The beginning dose of lead carbonate given *per os*

was 0.03306 Gm., gradually increased to 0.0909 Gm. In general, most of the kidneys showed fatty degenerative infiltration. In a guinea-pig that received the largest amount of lead carbonate (7.28018 Gm.) and that lived for 202 days after the beginning of the experiment, the typical fine granular surface of secondary contraction was found. As shown by microscopic examination, the initial changes were a slight parenchymatous degeneration of the tubular and glomerulocapsular epithelium, most distinct in the case of the proximal convoluted tubules, and extreme active and passive congestion. There were a few hyaline and granular casts in Henle's loops and in the collecting tubules. In several kidneys, epithelial desquamation occurred, and in three instances epithelial casts were present. Deposits of lime salt, first in the tubular casts and later in the adjoining epithelial cells and interstitial tissues, were present almost invariably in the loops of Henle and the collecting tubules. Fatty degenerative infiltration was a characteristic early manifestation which was most marked in the ascending limb of Henle's loops, the distal convoluted tubules and the papillary ducts. In addition to the aforementioned degenerative changes, regeneration of the damaged epithelial cells was observed. No degenerative or proliferative vascular lesions were found during the six or seven months of experimental time when the epithelial lesions are demonstrable. Interstitial fibroblastic proliferation was observed in the four animals that lived longer than six months and that received the largest amounts of lead carbonate (6.27 to 7.28 Gm.). The renal changes do not depend exclusively on the amount of lead given and the length of the experimental period. Individual susceptibility or resistance is apparently an important factor.

WALTER M. SIMPSON.

ADDISON'S DISEASE IN ASSOCIATION WITH AMYLOIDOSIS. N. W. PHILPOTT, Ann. Int. Med. **1**:613, 1928.

Philpott reports a case of amyloidosis which involved the suprarenal glands, and particularly the medulla and inner portion of the cortex, and which was associated with Addison's disease. The amyloid showed peculiar distribution elsewhere in the body; it involved the thyroid gland, pars intermedia of the hypophysis, heart and sympathetic nervous system, as well as the lungs, spleen, pancreas, retroperitoneal vessels and the larger vessels of the hepatic trinity. There was no active pulmonary tuberculosis, but there was the following abundant evidence of old syphilis: gummatous myocarditis, syphilitic pancreatitis, aortitis and adrenalitis. The literature contains but five other instances of Addison's disease associated with amyloidosis of the suprarenal gland.

WALTER M. SIMPSON.

EXPERIMENTAL STUDY OF ACQUIRED RESISTANCE OF THE RABBIT'S RENAL EPITHELIUM TO URANYL NITRATE. W. C. HUNTER, Ann. Int. Med. **1**:747, 1928.

When 0.001 Gm. of uranium nitrate is administered subcutaneously, or one half of this amount intravenously, into a normal rabbit, unmistakable histologic evidence of acute renal injury is manifested by: necrosis of the epithelium of the distal and transitional segments of the proximal convoluted tubules, swelling and desquamation of the glomerular epithelial cells, hemorrhage into the capsular space, intraglomerular hemorrhages and hyaline droplet degeneration of the glomerular capillary endothelium.

In the chronic stages, uranium produces a glomerulotubular nephritis which simulates that seen in the human being. Regeneration begins early in the epithelium of the glomerular tufts and Bowman's membrane. This regenerative process is frequently excessive and results in the formation of epithelial crescents, complete obliteration of the capsular space and resultant glomerular atrophy and hyaline degeneration. The regenerative ability of the tubular epithelium is even more remarkable, particularly when the dosage of uranium is carefully graduated and sufficient time elapses for more or less complete restoration between injections.

Hunter finds proof that the regenerated glomeruli and tubules have acquired an immunity for the nephrotoxic agent in their ability to tolerate larger subsequent

doses of uranium. Evidence that uranium still passes through the kidney with chronic injury is shown by necrosis of the epithelium in segments of the proximal convoluted tubules which are not injured until large amounts of uranium are administered. Biologic and qualitative tests on the urine of immunized rabbits show that the kidneys are capable of excreting rapidly considerable amounts of the metal. Many rabbits were given doses of uranium from fifty-four to ninety-six times greater than the quantity known to produce renal damage in a nonimmunized animal, without evidence of renal injury. As to the mechanism of the immunity, Hunter assumes that the regenerated epithelium is able to prevent the poison from uniting with the cell protein.

WALTER M. SIMPSON.

HISTOLOGIC CHANGES IN PERIPHERAL ARTERIES AND ARTERIOLES IN AMBULATORY CASES OF HIGH BLOOD PRESSURE. J. W. KERNOLIAN, E. W. ANDERSON and N. M. KEITH, J. Clin. Investigation **6**:4, 1928.

Cases of malignant hypertension showed, as the significant histologic picture, a diffuse arteriolar lesion. Biopsy material from the pectoral muscle of ambulatory patients with high blood pressure gave distinct thickening of the walls of the smaller arteries and arterioles, hypertrophy of the muscular elements of the media, especially, and hypertrophy of the internal elastic lamina. Perivascular fibrosis was not constant. The lining of endothelium in these vessels showed varying degrees of hyperplasia. As in tissues examined at autopsy, the endothelial hyperplasia was not particularly constant in cases of malignant hypertension. Results of the microscopic examination were compared with those of examinations of the eyeground; the appearance of the capillaries of the nail-fold was studied together with other clinical data.

H. R. FISHBACK.

OBLITERATIVE BRONCHIOLITIS IN ADVANCED RENAL DISEASE. E. G. STILLMAN, W. E. EHRLICH and J. F. MCINTOSH, J. Clin. Investigation **6**:5, 1928.

Three cases of advanced renal disease, ending in death from uremia showed serositis and fresh indication of bronchopneumonia. Older lesions in various stages of organization also were observed in the bronchioles and alveoli. The pathologic picture differs from that of obliterative bronchiolitis after infectious disease or the inhalation of poisonous gases. Roentgen-ray examination showed a characteristic, reticular marking of the region of the hilum.

H. R. FISHBACK.

PLEURAL AND PULMONARY LESIONS IN RHEUMATIC FEVER. J. R. PAUL, J. Clin. Investigation **6**:6, 1928.

In twenty-eight patients dying during the active stages of rheumatic fever, atelectasis of varying degree was found in the dependent portions of both lungs and almost always in the left lung. This seemed to be related to pleurisy and the presence of an enlarged pericardial sac. Sixty per cent of the cases showed evidences of pleurisy. It resembles rheumatic pericarditis, although less serious, and may be an extension of that process. The pleural fluid was rich in fibrin, with few polymorphonuclear cells and many mononuclear and endothelial cells. Bacteria were not found. Vascular lesions of a specific nature were present in 30 per cent of the cases. The lesion is a panarteritis with primary involvement of the endothelium. Hemorrhagic bronchopneumonia was shown in more than half the cases, especially in those in which the patients were under twenty years of age. There were multiple hemorrhagic foci in the lungs, in which bacteria could not be demonstrated. This was a possible manifestation of purpura.

H. R. FISHBACK.

GOITER IN LABORATORY ANIMALS. A. M. CHESNEY, B. WEBSTER and T. A. CLAWSON, J. Clin. Investigation **6**:8, 1928.

A high incidence of goiter has been observed in 486 rabbits under observation for varying periods over four years. The goiter was not related to any breed but

was definitely related to the length of time the animals had been caged. It developed in animals used in the study of syphilis and in normal controls.

The thyroid enlargement was diffuse. There was marked hyperplasia, and lessened colloid. Many died in a cachectic state without signs of terminal infection. Goitrous animals had an average depression of heat production of 16 per cent below that of normal animals. In some animals, the rate increased prior to death. The daily administration of 1 minim (0.06 cc.) of Lugol's solution by mouth resulted in a prompt increase in the metabolic rate, rapid loss of weight, and death within a few days. In these animals there was indication of newly deposited colloid in the thyroid. Such reactions were not obtained in normal rabbits with the administration of iodine.

H. R. FISHBACK.

THE ARTERIAL SUPPLY OF THE CONGENITAL POLYCYSTIC KIDNEY. G. BAEHR and S. A. RITTER, J. Clin. Investigation **6**:19, 1928.

The clinical course of patients with bilateral cystic kidneys may be uneventful until late in adult life, but attacks of lumbar pain commonly occur, sometimes followed by persistent hematuria. By the method described, barium sulphate and gelatin are injected into the arterial supply of the kidneys; after the organs are cleared in methyl salicylate, they are studied by stereoroentgenograms. The arteries in the walls of the cysts are found to be stretched, and sometimes extend across the cavities, enveloped in a thin falciform fold of the cyst wall. Rupture of these arteries occurs from various causes resulting in a hemorrhagic cyst. If this cyst ruptures into a calyx, hematuria occurs; if it ruptures at the surface of the kidney, a perirenal hematuria is produced. Sclerosis of the arterioles or small arteries of the kidneys and other organs develops usually in the third decade, but occasionally as late as the sixth decade of life. This gives the same clinical picture in its evolution as primary arteriosclerosis, or the late stage of chronic glomerulonephritis following nephritic edema.

H. R. FISHBACK.

THE SURGICAL PATHOLOGY OF MALFORMATIONS IN THE KIDNEYS AND URETERS. JAMES E. DAVIS, J. Urol. **20**:1 and 155, 1928.

These articles review the development of the urinary excretory processes from the lowest to the highest forms of life, the comparative anatomy of the kidneys and the malformations in domestic and wild animals and man, with particular reference to the congenital cystic kidney. Twenty instances of cystic kidneys in human beings are described.

SUPRARENAL-RENAL HETEROTOPIA. HAROLD D. CAYLOR, J. Urol. **20**:197, 1928.

Another case of suprarenal-renal heterotopia is added to the thirteen reported. The anomaly is frequently bilateral, and during nephrectomy it is almost inevitable that the suprarenal gland will be removed and that acute deficiency in epinephrine will result. The disorder frequently is associated with status thymicolymphaticus with the accompanying susceptibility to surgical shock and infection.

AUTHOR'S SUMMARY.

PAPILLARY CARCINOMA OF THE KIDNEY WITH CYST, CONTAINING OVER EIGHT LITERS OF FLUID. GEORGE F. CAHILL and HAROLD H. GILE, J. Urol. **20**: 203, 1928.

A case is reported of papillary carcinoma of the kidney, remarkable for its large cystic formation.

AUTHORS' SUMMARY.

MUCIPAROUS GLANDS IN THE MUCOSA OF THE URINARY BLADDER. LEO EDELMAN, J. Urol. **20**:211, 1928.

The question of the presence of mucous glands in the urinary bladder is still open. Some observers deny they exist; some admit their presence, and others

interpret them as aberrant prostatic or urethral glands. The cases reported in the literature showing lesions containing "intestine-like" mucous glands, have their origin ascribed to: misplaced embryonal intestinal glands (exstrophy); embryonal rests; proliferation and metaplasia of the surface epithelium (Enderlen); proliferation of lesions in cystitis cystica, due to an inflammatory process (Stoerk and Zuckerkandl), and proliferation of mucous glands normally present in the mucosa (Bridoux). The lesions have no distinctive symptomatology. The patients usually complain of frequency, dysuria and hematuria. The diagnosis can be made only by microscopic examination of the tissue removed. The treatment is either excision or destruction with the cautery. The persistence of these glands may possibly be the basis for the development of adenomas or adenocarcinoma.

AUTHOR'S SUMMARY.

DIAGNOSIS OF BRANCHIAL CYST. H. BAILEY, Brit. M. J. **1**:940, 1928.

If the fluid contains numerous cholesterol crystals, the diagnosis of branchial cyst is certain.

MULTIPLE TRAUMATIC ABDOMINAL ANEURYSMS. J. MCFADZEAN, Brit. M. J. **2**:154, 1928.

A senile dement, with extremely grandiose ideas but without clinical or serologic evidences of syphilis, who for twenty years had spent one-half hour a day as an acrobat, rolling around a hard trapeze on his abdomen, died suddenly one morning on attempting to get up. Some time previously an expansive, pulsating abdominal tumor had been diagnosed as an aneurysm. The autopsy disclosed that the abdominal part of the aorta and the greater part of the common and external iliac arteries were degenerated, calcified and irregularly dilated and that four aneurysms occupied most of their extent. The thoracic part of the aorta and certain other large arteries were less atheromatous than could be expected for the man's age. Evidences of syphilis were not found in the postmortem examination. The theory is advanced that the remarkable degeneration and formation of aneurysms resulted from repeated injuries by the trapeze.

GEORGE RUKSTINAT.

OBSERVATIONS ON RAT AND HUMAN LEPROSY. J. M. HENDERSON, Indian J. M. Research **16**:1 and 7, 1928.

Suspensions of material rich in the specific organism of rat leprosy were injected subcutaneously in white rats. The subsequent lesion spread along the lymphatic planes between the corium and the subcutaneous tissue. The reaction was principally lymphocytic in character; giant cells were absent. In human leprosy, large multinucleated cells seem to be more common than is generally supposed.

ADIPOSITAS DOLOROSA AND DERCUM'S DISEASE: ITS CELLULITIC PATHOGENESIS. GUY LAROCHE, Ann. de méd. **23**:445 1928.

Laroche believes that the pain associated with the obese condition in Dercum's disease is due to a subcutaneous cellulitis which, he asserts, arises from the fixation of some irritating products in the tissues. Dercum's disease, then, may be included in the "neuro-arthritic" group of diatheses, such as gout and chronic rheumatism. Laroche bases his opinion on clinical observations; he does not produce any microscopic documents.

B. M. FRIED.

METAL CORROSION USED IN MODELS OF BRONCHI AND CAVITIES IN PHTHISICAL LUNGS. R. STEINERT, Beitr. z. Klin. d. Tuberk. **68**:199, 1928.

Eight models employing metal corrosion are reproduced to show the size, shape and localization of tuberculous cavities, their relation to bronchi, and the occasionally extreme distortion of the bronchi.

MAX PINNER.

PROPERITONEAL CYST IN ANTERIOR ABDOMINAL WALL. E. UTTERSTRÖM and H. BERGSTRAND, Upsala Läkaref. Förh. **34**:403, 1928.

A woman, aged 29, had had a tuberculous disease of the foot in childhood, now completely healed, and steady enlargement of the abdomen with a feeling of oppression for the previous two years. An operation disclosed a thin-walled, flaccid, properitoneal cyst extending throughout the abdominal cavity. Tuberculosis was not demonstrable in the wall of the cyst. Utterström believes that the cyst developed from a formation in the median vesico-umbilical ligament and is inclined to regard it as originating from a urachal remnant. Bergstrand presents the results of his microscopic examination.

TISSUE REACTION TO IODIZED OIL. C. GRILL and K. G. KLING, Upsala Läkaref. Förh. **34**:459, 1928.

Grill and Kling studied the reaction in the lungs of six rabbits up to six months after the injection of 1 cc. of iodized oil. Microscopic examination showed the iodized oil to be chiefly in the small bronchi, blocking them and causing partial atelectasis, which in the author's opinion predisposes to inflammatory processes and constitutes one of the dangers in the introduction of iodized oil into the air passages for diagnostic or therapeutic purposes.

Pathologic Chemistry

ARSENIC IN ARSENICAL DERMATITIS. EARL D. OSBORNE, Arch. Dermat. & Syph. **18**:37, 1928.

The arsenic in quantivalent compounds has a special affinity for ectodermal structures, while the arsenic in trivalent compounds has a special affinity for vascular structures.

CHOLESTEROL AND CHOLESTEROL ESTER CONTENT OF BOVINE COLOSTRUM AND BLOOD SERUM. RICHARD E. SHOPE and JOHN W. GOWEN, J. Exper. Med. **48**:21 and 25, 1928.

The total amount of cholesterol found in colostrum and milk is comparatively low. The amount of cholesterol found in colostrum declines at an ever decreasing rate as the secretion of milk develops, until at forty-eight hours the cholesterol is nearly the same as that found in milk three or seven months after parturition. The morning milk differs from the evening milk in that the cholesterol bound as ester is great in amount. The total cholesterol and cholesterol ester of bovine blood serum during the "dry" period of late pregnancy is low. Following parturition, the total cholesterol and cholesterol ester of bovine blood serum shows a still greater, transient decrease followed by a gradual rise to reach a rather constant level from forty to fifty days post partum. This lactation level is much higher than the "dry" level.

AUTHORS' SUMMARY.

LOOSELY BOUND SULFUR IN PITUITARY EXTRACTS. M. X. SULLIVAN and M. I. SMITH, Pub. Health Rep. **43**:1334, 1928.

Another physiologic property has been correlated with an accurately measurable chemical property. Extracts of the posterior pituitary lobe yield precipitates of lead sulphide when warmed with dilute alkali and lead acetate, which appear to be proportional in magnitude to the capacity of the preparation to produce an elevation of blood pressure on injection into anesthetized dogs. (A similar relation between hypoglycemic activity and labile sulphur content was suggested for the hormone insulin by Abel and Geiling, *J. Pharmacol & Exper. Therap.* **25**:423, 1925.)

ARTHUR LOCKE.

THE BLOOD CHOLESTEROL IN NEPHRITIS. J. MAXWELL, Quart. J. Med. **21**:297, 1928.

Edema of the suprarenal gland is almost invariably associated with an increase in the plasma cholesterol. This increase may not be great, but even the slighter degrees are shown to be of definite significance, because the cholesterol decreases as the edema disappears. This is seen most clearly in cases of acute nephritis. In cases of acute nephritis with edema the plasma cholesterol is raised in degree proportionate to the edema. During recovery the edema first clears up, the plasma cholesterol next returns to normal, and then usually becomes subnormal for a short time, and finally the albumin practically disappears from the urine. In a case of apparent acute nephritis of this type the persistence of the plasma cholesterol above normal indicates a chronic course of the disease. In acute nephritis without edema the plasma cholesterol is not of any diagnostic or prognostic value. In chronic parenchymatous nephritis much higher cholesterol values are frequently found, and the amount of cholesterol increase is in no way proportional to the degree of edema. In cases of edema of doubtful origin, a high plasma cholesterol is a strong point in favor of the origin of the condition in the suprarenal gland if the other factors which may cause an increased cholesterol content in the blood can be excluded. Edema of the suprarenal gland and the increased plasma cholesterol are not related as cause and effect. Each is probably the result of some toxic process, acting on the tissue cells, particularly those of the reticuloendothelial system. A persistently raised plasma cholesterol in patients who have been free from edema for a long period is often associated with the onset of uremia. In uremia the cholesterol is usually normal or low. In pure chronic interstitial nephritis the cholesterol is normal or low. In primary arteriosclerosis the figures are usually higher. The edema of heart failure is not associated with a rise in cholesterol unless arteriosclerosis or some other factor is present.

N. ENZER.

OXYGEN AND CARBON DIOXIDE IN ARTERIAL AND VENOUS BLOOD IN PULMONARY TUBERCULOSIS. F. POMPLUN, Ztschr. f. Tuberk. **51**:185, 1928.

It was previously shown that the carbon dioxide content of arterial blood is frequently increased in pulmonary tuberculosis. Further studies led to the following explanation of this condition: In pulmonary tuberculosis the carbon dioxide is increased in the capillary system. The free carbon dioxide may be increased if an insufficient amount of alkali is present. Free carbon dioxide is increased when the oxygen supply is decreased on account of the presence of acids which bind the available alkali. The available alkali is represented in the hemoglobin, plasma proteins, phosphates and other proteins. They all may carry carbon dioxide to the arterial circulation, if they are not neutralized by other acids. Destruction of pulmonary tissue causes a decrease in oxyhemoglobin. All these factors, however, will not cause an increased carbon dioxide content in the arterial blood unless there is a sufficient amount of pulmonary destruction to prevent a sufficient elimination of carbon dioxide. The increase of carbon dioxide in the arterial blood becomes the greater the longer the various factors already enumerated exist. In such cases both the free carbon dioxide and the bicarbonates are found to be increased.

MAX PINNER.

Microbiology and Parasitology

THE ETIOLOGY OF AN EPIDEMIC OF ENTERITIS ASSOCIATED WITH MASTOIDITIS IN INFANTS. GEORGE F. DICK, GLADYS HENRY DICK and J. L. WILLIAMS, Am. J. Dis. Child. **35**:955, 1928.

Bacteriologic examinations during an epidemic of enteritis associated with mastoiditis in infants revealed the disease to be primarily an intestinal infection with the Morgan dysentery bacillus. The epidemic was controlled by discarding all foods which were not fresh and which could not be boiled, and by preventing the transfer of intestinal bacteria by the fingers of nurses.

PEARL ZEEK.

A Fulminating Case of Tularemia. H. D. Palmer and G. H. Hansmann, J. A. M. A. **91**:236, 1928.

The only complicating feature in this case (the woman died ten days after infection) was an inconsiderable amount of bronchopneumonia which did not give any clinical symptoms. This was not considered to have any appreciable effect on either the length of life of the patient or the acuteness of the lesions other than those in the lung.

The localization of the organisms with the production of lesions was limited to the finger, axillary lymph nodes, spleen and liver. Individual lesions showed the central area of necrosis with fibrin deposit and the peripheral endothelial cell reaction described in the lesions of case 10, which represents the earliest lesion studied by Francis and Callender. The authors' case differs, however, in that giant cells were not found; there was no appreciable thickening of the blood vessel walls about the lesion, and there was marked fatty degeneration of the endothelial cells.

Cell changes, other than those participating in the formation of discrete lesions, suggested the presence of a strong toxin. All tissues were involved in an acute degeneration of the parenchymatous and endothelial elements. Attention is directed particularly to the fat found in the endothelium of the glomerular tufts, in the renal epithelium, in the muscle cells of the vessels and in the cellular elements of the central nervous system. There was also an acute degeneration of the myelin in the central nervous system. This was the only cause that could be found to account for the sudden and complete deafness.

Authors' Summary.

Mercurochrome and Iodine as Disinfections of Skin and Oral Mucous Membrane. James S. Simmons, J. A. M. A. **91**:704, 1928. F. E. Rodriguez, ibid., p. 708. C. F. Reddish and W. E. Drake, ibid., p. 712.

Simmons found that tincture of iodine (U.S.P.) was far superior to 2 per cent aqueous solution, to 2 per cent alcohol-acetone-aqueous solution and to 5 per cent alcoholic solution of mercurochrome. Rodriguez found that iodine "in dilutions of 3.5 per cent, and even in 1.75 per cent strength, preferably in glycerin, is an effective germicide" for the oral mucous membrane. Mercurochrome was not uniformly effective in 2 per cent and 5 per cent solutions. Reddish and Drake, on the other hand, hold that 2 per cent mercurochrome in aqueous-alcohol-acetone solution is preferable to tincture of iodine for preoperative disinfection of the skin.

Experimental Intradermal Pneumococcus Infection in Rabbits. Kenneth Goodner, J. Exper. Med. **48**:1, 1928.

The intradermal inoculation of rabbits with type 1 pneumococci gives rise to a local lesion and a definite sequence of other events that offer many analogies to pneumococcus lobar pneumonia, and for this reason the condition is being employed for a resurvey of the subject of pneumococci infection. This symptom-complex has been described in detail, particularly as to the development of the local lesion, the temperature reaction, the bacteremia, the white count, the persistence of organisms in the lesion and the development of protective substances. A certain number of animals recover from this condition after a definite course and by a process spoken of as crisis. The events correlated with this crisis have been described. If sufficient antipneumococcic serum is given intravenously twenty-four hours after infection, prompt recovery can be brought about. The essential points of this recovery have been established. Within five days after a single vaccination with dead pneumococci, the normal rabbit develops an immunity to infection. If the rabbit is vaccinated and then infected within the period necessary for the development of this immunity, the course of the consequent disease is shortened in proportion to the interval between vaccination and infection.

Author's Summary.

THE ETIOLOGY OF TRACHOMA. HIDEYO NOGUCHI, J. Exper. Med. **48**:1 (supplement 2), 1928.

1. *Investigations of Trachoma in American Indians.*—According to clinical and pathologic studies, the granular or follicular conjunctivitis prevailing among the American Indians at a reservation in New Mexico is to be classed with trachoma as observed in other parts of the world. Through the employment of particular kinds of culture mediums for inoculation with materials obtained from trachomatous eyes, and by the use of incubation at low temperatures, not only have a number of common bacterial forms — cocci, bacilli and sarcinae — been secured, but, in addition, two distinct varieties of peculiar gram-negative motile bacilli, from four of the five cases of trachoma studied bacteriologically. The two kinds of motile bacilli are readily distinguished, since one grows well at 37 C., as well as at lower temperatures, on ordinary culture mediums, while the other requires mediums containing animal blood and thrives best at temperatures of from 15 to 30 C. The latter organism does not multiply when oxygen is completely excluded. It resembles *Bacterium monocytogenes* but differs from the latter in its inability to grow on ordinary mediums at 37 C., in its nonpathogenicity for rabbits and in serologic reactions. Under conditions of multiplication considered unfavorable, the bacilli assume forms found in the group of corynebacteria, but differ from these in showing motility under certain conditions for growth. Single polar flagella are carried by the bacilli, which do not seem to have been described before. These bacilli take on a special significance in virtue of the fact, described in a later part of this report, that they are able to induce granular conjunctival inflammation on inoculation into monkeys. Because of this property, the name *Bacterium granulosis* is proposed for the organism. Unsuccessful attempts were made to induce trachoma in rhesus monkeys, a chimpanzee and an orang-utang, by direct inoculation of materials taken from the cases of trachoma in Indians described in this paper.

2. *Experimental Granular Conjunctivitis in Macacus Rhesus and Chimpanzee with Bacterium Granulosis,* N.Sp.—A study has been made of the pathogenic action of several kinds of micro-organisms cultured from cases of trachoma in Indians. These pure cultures, in heavy suspension, have been injected into the subconjunctival tissues of *Macacus* monkeys and the chimpanzee. With one notable exception, the cultures produced only fleeting reactions or acute inflammation, which soon subsided. The exception is notable, because the injection of the culture of a bacillus, called *Bacterium granulosis,* n. sp., induced a persistent granular conjunctivitis resembling closely, and apparently identical with, trachomatous granular conjunctivitis in man. It is noteworthy that when the granular condition was induced in one eye by the injection, spontaneous infection, attended by granular conjunctivitis, followed in the other eye, and when the tissues from a slowly progressing granular conjunctivitis in one eye were removed and inoculated into the conjunctiva of the other side, a more rapidly advancing granular conjunctivitis of this side was produced. The histologic changes of the experimentally induced conjunctival lesions correspond closely with those of trachoma in man and include the characteristic follicle and scar tissue formation.

3. *Transmission of Experimental Granular Conjunctivitis.*—A series of transfers of the granular conjunctival lesions, directly induced by inoculation of culture, from animal to animal were made in lower monkeys and in the chimpanzee. Six monkeys of the species *Macacus rhesus,* originally inoculated with the cultures of *Bacterium granulosis,* supplied the material for the inoculation of twenty-four lower monkeys, consisting of twenty-three of the species *Macacus rhesus* and one Japanese monkey *(Macacus speciosus).* Positive results in transmission were obtained in twenty rhesus monkeys and one Japanese monkey. Three rhesus monkeys proved entirely refractory to one transfer, and the remaining rhesus monkey gave a doubtful result. From three rhesus monkeys (nos. 30, 45, and 69) in which successful transfers had been made, two chimpanzees, eighteen rhesus monkeys, two baboons and one orang-utang were inoculated. With the material from rhesus monkey 30, the transfer was highly successful in one chimpanzee,

and partially successful in the other chimpanzee and in one of two of the species *Macacus rhesus*. Material taken from rhesus monkey 45 yielded marked lesions in one rhesus monkey and one baboon, and mild lesions in two rhesus monkeys. The results were entirely negative in eight rhesus monkeys, one baboon and one orang-utang. Two rhesus monkeys inoculated with material from rhesus monkey 69 also failed to react. On the other hand, the transfer of material taken from the chimpanzee produced typical granular lesions of the conjunctiva in one rhesus monkey when the chimpanzee lesion was forty-nine days old, and in two other rhesus monkeys when the lesions were 151 days old. With the latter material a chimpanzee was also successfully inoculated. A fourth passage with material obtained from this animal was successful in four macaques and in another chimpanzee.

4. *Bacterium Granulosis in the Experimental Lesions and in Lesions in Man.*—The experimental chronic granular conjunctivitis first induced in *Macacus rhesus* with pure cultures of *Bacterium granulosis*, were transferred by direct tissue passage to the chimpanzee, to the baboon and to other monkeys of the species *Macacus rhesus* through at least four successive passages. This experimental chronic granular conjunctivitis preserved the clinical and histologic characters throughout the several passages, and the lesions were shown to be infective as early as 17 and as late as 204 days after the original culture inoculation. Bacterium granulosis can be recovered from the inoculated animals and has been found in microscopic specimens of human and monkey tissues. The great difficulty of its recovery in culture and its demonstration in sections of tissues and in films is not necessarily an indication of its absence from the lesions. The methods employed to recover or to find the organism may not be the most favorable to be discovered. No other micro-organism obtained from the cases of trachoma in man produces effects in animals comparable to those induced by *Bacterium granulosis*. In the absence, therefore, of indications to the contrary, one may consider that in *Bacterium granulosis* one finds the inciting micro-organism of trachoma in man and its equivalent, granular conjunctivitis in monkeys.

AUTHOR'S SUMMARIES.

THE INCUBATION PERIOD OF YELLOW FEVER IN THE MOSQUITO. JOHANNES H. BAUER and N. PAUL HUDSON, J. Exper. Med. **48**:147, 1928.

The virus of yellow fever was found in infectious form in *Aedes aegypti* throughout the entire period of the extrinsic incubation, as demonstrated by the injection of the bodies of mosquitoes into normal rhesus monkeys at daily intervals after the insects had fed on an infected animal. The virus was transmitted through the bite of the mosquitoes — in one experiment on and after the ninth day, and in two experiments on the twelfth day, after the initial infecting feed. The pathologic changes produced by the injection of the infected mosquitoes into normal monkeys during the extrinsic incubation were, in every respect, those of typical experimental yellow fever. The monkeys withstand easily the subcutaneous injection of the mosquito emulsion. An acute inflammatory reaction was not observed at the site of injection in any of the seventeen animals inoculated with this material in the three experiments.

AUTHORS' SUMMARY.

THE FATE OF HUMAN AND BOVINE TUBERCLE BACILLI IN VARIOUS ORGANS OF THE RABBIT. MAX B. LURIE, J. Exper. Med. **48**:155, 1928.

The original distribution of tubercle bacilli of both human and bovine types to the various organs of the rabbit after intravenous inoculation follows the distribution of particulate matter in the following order per gram of tissue; spleen, liver, lung, bone marrow and kidney. The relative position of the lung among these organs is less certain than that of the other organs. At first, the tubercle bacilli of both human and bovine types grow in all the organs without any effective opposition. The rate of growth of both types differs in the various organs. It is much faster in the spleen than in the liver. With small doses, little growth takes

place in the liver and bone-marrow, especially with the bovine type. The type of tubercle bacillus found in man grows faster in the several organs of the rabbit and is followed by an earlier and more complete destruction than the bovine type. With both types, destruction occurs first in the liver, spleen and bone-marrow. In the lung and kidney, destruction of the type found in man takes place later, but unchecked multiplication of the bovine type continues until the death of the animal. With smaller doses of the bacilli found in man, destruction is brought about later in the liver, spleen and bone-marrow than with larger doses. With both types, in a given time, destruction is more complete in some organs after a large dose than after a small dose. The destruction in the various organs is rapid at first, and progresses more slowly as time passes. Even six months after the intravenous injection of small doses of tubercle bacilli found in man, the organisms have not yet completely disappeared from the lung and spleen.

AUTHOR'S SUMMARY.

THE EFFECT OF CHEMICAL CONSTITUENTS OF TUBERCLE BACILLI ON AMOEBA DUBIA. PAUL REZNIKOFF, J. Exper. Med. **48**:193, 1928.

Protein fractions derived from tubercle bacilli are toxic to the interior of *Amoeba dubia* but do not have any action on the plasmalemma. Phosphatide fractions dissolve the plasmalemma but do not have any effect on the internal cytoplasm. The fatty acid fraction has a marked solvent action on the plasmalemma when brought in contact with the surface of the cell. When injected, it may slowly penetrate the cytoplasm to dissolve the contiguous plasmalemma. The polysaccharide fraction does not have any effect on the surface membrane or on the internal cytoplasm of *Amoeba dubia.*

AUTHOR'S SUMMARY.

THE RELATION OF STREPTOCOCCI TO HERPES VIRUS ENCEPHALITIS. PETER K. OLITSKY and PERRIN H. LONG, J. Exper. Med. **48**:199, 1928.

Cultures of micro-organisms similar to those described by Evans have been obtained in mediums inoculated with suspensions from brains infected with the herpes virus, which have been prepared by grinding. But they have also been isolated from saline suspensions of uninoculated meat particles ground in a sterile mortar, and from dextrose broth treated in the same way. It is believed that these organisms are contaminants introduced during the process of grinding. Since they do not enter the material in any great number, one may suppose them to be suppressed by animals inoculated with the ground substance. In artificial mediums, on the other hand, they find favorable conditions for multiplication. In our experience, a growth of micro-organisms is not obtained in routine cultures of brains infected with a virus, when fragments, instead of ground material, are used—a fact which may be taken to support the explanation just given. The tests of the part played by streptococci in experimental cases of encephalitis due to infection with a virus failed to disclose that the micro-organisms have any etiologic relationship to the condition. The intracerebral injection of rabbits with the cultures procured in the course of the experiments produces a purulent type of meningo-encephalitis which does not resemble virus encephalitis either in its symptom-complex or in its pathologic changes. The same type of meningitis follows the injection of streptococci derived from ground meat particles, from "ground" broth, from normal brains and from brains infected with herpes virus. Some rabbits manifested resistance to the streptococci, whereas all that were inoculated intracerebrally with the three strains of herpes virus used in this study proved susceptible thereto. Certain of the rabbits just mentioned which had proved resistant to streptococci inoculated into the brain or cornea were injected with herpes virus and reacted typically. Comparative tests have revealed that the streptococci are more sensitive to the destructive effect of 50 per cent glycerol than is herpes virus. From all this, it can be concluded that streptococci are not the visible form of herpes virus, nor do they produce in rabbits effects like those induced in the brain and cornea by the herpes virus.

AUTHORS' SUMMARY.

THE SANITARY SIGNIFICANCE OF LACTOSE-FERMENTING BACTERIA NOT BELONGING TO THE B. COLI GROUP. FRANK E. GREER and COWORKERS, J. Infect. Dis. **42**:525, 537, 545, 556 and 568, 1928.

It is pointed out that there are other organisms found in water which ferment lactose besides *Bacillus coli.* Some of these should be considered in judging the sanitary quality of water. This is especially true of *Streptococcus fecalis. Clostridium welchii,* Friedländer's group and *Pseudomonas pyocyaneus* may also be of sanitary significance. All mediums that have been developed so far have their limitations. A promising field of work for the future is the developing of direct plating methods for the detection and enumeration of these organisms.

AUTHORS' SUMMARY.

MICROBIC DISSOCIATION OF B. COLI-COMMUNIS. ANNA DEAN DULANEY, J. Infect. Dis. **42**:575, 1928.

Microbic dissociation has been produced in *Bacillus coli-communis,* and the chief dissociants have been studied. The S and R forms show a distinct and characteristic difference in the form of the colonies and the morphology of the cells. The O form represents an intermediate stage, and resembles S or R, according to the length of time of cultivation on phenol medium. The S→R change may be produced by aging, provided the ultimate reaction of the medium is alkaline, and by the cultivation in S-immune serum. The R→S change is obtained with greater difficulty by the use of R-immune serum. Dissociation is inhibited by the use of sugar producing an acid medium. The cultural reactions of S and R forms differ but slightly, yet immunologically R antiserums agglutinate only R forms, and in cultures of S forms there is a soluble substance which reacts only with S antiserums. A corresponding soluble substance is not demonstrable in R cultures.

From AUTHOR'S SUMMARY.

EFFECT OF DIETS DEFICIENT IN VITAMIN A OR B ON RESISTANCE TO PARATYPHOID ENTERITIDIS ORGANISMS. ELIZABETH VERDER, J. Infect. Dis. **42**:589, 1928.

Examination of six rats on vitamin B-free rations and of six rats on vitamin A-free rations which were killed from eighteen to forty-eight or ninety-six hours after being fed suspensions of *Bacillus enteritidis* revealed organisms in the spleens of five rats on the vitamin A-free diet and in the intestinal tract of all rats, but not in the heart blood, liver or kidneys of any rat. Organisms of the paratyphoid enteritidis group were not isolated from rats on the same diet, without the suspension of *B. enteritidis.* Simmon's citrate agar was used successfully for the isolation of *B. enteritidis* from fecal suspensions.

From AUTHOR'S SUMMARY.

THE EPIDEMIOLOGY OF UNDULANT FEVER IN IOWA. A. V. HARDY, Pub. Health Rep. **43**:2459, 1928.

In a summary of the epidemiology of undulant fever in man Hardy discusses the possible sources of infection, distribution according to various factors and accuracy of diagnosis. The latter is based on the variable clinical symptoms and on the serology. It is suggested that the disease is much more widespread than is generally supposed and in this respect is compared with typhoid and paratyphoid infection by serologic means.

"FRUIT POISONING": AN INVESTIGATION OF ITS ETIOLOGY, SYMPTOMATOLOGY AND PATHOLOGY, WITH SUGGESTIONS AS TO TREATMENT. L. B. KINGERY, Warthin Ann. Vol., 1927, p. 49.

An occupational dermatosis, known among cannery workers as "fruit poisoning," has existed in certain portions of the Northwest for at least five or six years. The incidence is estimated to be as high as 33.3 per cent of those employed as

handlers of fruit. The symptomatology consists of marked paronychia, characterized by inflammatory reaction, pain and loss of one or more finger nails. In addition, maceration, vesiculation and fissuring between the interdigital aspects of the fingers is frequently found, together with occasional patches of erythematovesicular dermatitis on the hands and forearms. The course of the disease is acute during the pear season.

Cultures from several patients have uniformly revealed pure cultures of a yeastlike organism. Inoculations in animals and in man with organisms thus obtained result in a clinical picture practically identical with known mycelial infections of the skin. It would seem that so-called "fruit poisoning" may be properly classified with the dermatomycoses.

WALTER M. SIMPSON.

CLASSIFICATION OF CERTAIN GRAM-NEGATIVE COCCI IN THE NASOPHARYNX. S. P. WILSON, J. Path. & Bact. **31**:477, 1928.

Six different strains of gram-negative cocci from the respiratory tract were kept in artificial culture for periods ranging from a few weeks to a year. At frequent intervals, these organisms were submitted to a series of tests relating to their colonial morphology, growth in broth, growth on agar, growth at room temperature and fermentation reactions. Though the characteristics of the different strains often remained constant for a considerable time, eventually no fewer than five of the six underwent variation in one or more respects. The most frequent variation noted was a change in the appearance of the colony from smooth to rough or from rough to smooth. Two strains showed variability in their growth in broth, four strains variability in their growth at room temperature and two strains variability in their fermentation of sucrose. The six strains may probably be divided into three groups, each group consisting of two strains. Of eighty-five strains of gram-negative cocci, other than the meningococcus and *Micrococcus catarrhalis*, collected at random, sixty-seven could be related to one or other of the standard strains and eighteen strains showed such diverse characteristics as to prevent their being classified in any of our groups. None of the author's standard strains could be identified with any of the classic species of gram-negative cocci. It is suggested that this group of organisms is subject to a considerable range of variability and that classification on the basis of colonial appearances is open to serious objections. It seems probable that the gram-negative cocci of the nasopharynx form a single species within which are a few more or less constant subspecies, each of which is itself subject to variation. Until more is known of the extent of this variation, it does not seem justifiable to assign specific names to the numerous types that have from time to time been described by different investigators.

AUTHOR'S SUMMARY.

A CASE OF CONTINUED FEVER DUE TO B. ALKALESCENS (EBERTHELLA ALKALESCENS) ANDREWES. J. SMITH and A. M. FRASER, J. Path. & Bact. **31**:511, 1928.

In a woman, aged 20, the first symptoms appeared two days after confinement. The organism was isolated from the feces, urine, uterine secretions and blood.

THE GASTRO-INTESTINAL FLORA IN PERNICIOUS ANEMIA. L. S. P. DAVIDSON, J. Path. & Bact. **31**:557, 1928.

Evidence was not found to indicate that any individual type of organism was specifically related to pernicious anemia, or that bacterial hemolysins are of etiologic importance in the disease. A great numerical increase of organisms, normal inhabitants of the bowel (e. g., *Bacillus coli*, streptococci and especially *Bacillus welchii*) was found to occur in the gastro-intestinal contents in cases of pernicious anemia. Evidence was not found that these organisms differed

qualitatively from those found in healthy persons. The great quantitative increase of bacteria, especially at levels of the small intestine which in normal persons are relatively bacteria-free, is a factor of great etiologic importance.

AUTHOR'S SUMMARY.

ANIMAL EXPERIMENTS AND SPRUE. F. P. MACKIE and G. D. CHITRE, Indian J. M. Research **16**:49, 1928.

Sprue has not been produced in monkeys or other laboratory animals.

OBSERVATIONS ON CERTAIN TREPONEMAS. A. BESSEMANS, Arch. internat. de méd. expér. **3**:741, 1927.

The author presents experimental evidence to support the view that, on the one hand, the treponema cultivated by Noguchi, and, on the other, the neurotropic virus of Levaditi and *Treponema cuniculi* are, at least, distinct varieties of *Treponema.*

PEARL M. ZEEK.

SODOKU (RAT-BITE FEVER). J. SCHOCKAERT, Arch. internat. de méd. expér. **4**:133, 1928.

This article, which covers nearly 100 pages, gives a complete review of rat-bite fever, including the recent observations on the effect of producing this fever by inoculation in patients with paresis. The different strains of spirillum observed in this disease in man, rats and mice are regarded as constituting a single species (*Spirillum minus*). While infection with *Spirillum minus* influences favorably the course of paresis, it does not exercise any such action on trypanosomiase as that produced by *Spirochaeta duttoni.*

STUDIES ON THE PRIMARY TUBERCULOUS FOCUS IN THE LUNG. E. SCHULZE, Beitr. z. Klin. d. Tuberk. **68**:216, 1928.

Eighteen cases of primary foci in children up to the age of 12 years were examined. Detailed histologic studies were made in regard to the description of such foci as given by Ranke. The conclusions drawn from this work were that Ranke's statements were essentially correct, barring a few minor details.

MAX PINNER.

DEVELOPMENT, SCARRING AND REACTIVATION OF PULMONARY TUBERCULOSIS IN ADULTS. H. LOESCHCKE, Beitr. z. Klin. d. Tuberk. **68**:251, 1928.

In disagreement with numerous clinical publications during the last few years, the author maintains that pulmonary tuberculosis in the adult begins regularly in the apexes. The apical scars show intra-acinous development, indicating reinfection with small amounts of bacilli. From such scars, further spread occurs. This consists either of small slowly progressing apicocaudal lesions or of larger foci. The latter occur when the process breaks into a bronchus. The clinical appearance of these foci is Assmann's "infraclavicular infiltration." They are caseous pneumonic foci, which either excavate or become encapsulated. The reactivation of encapsulated chalky material occurs either by migration through the capsule in lymph channels and the rupture of bacilli into neighboring acini, or by rupture of the capsule into a bronchus, giving rise to larger foci and to the formation of a heavily encapsulated cavity.

MAX PINNER.

SEDIMENTATION REACTION, MATÉFY REACTION AND ARNETH COUNTS IN PULMONARY TUBERCULOSIS. E. KRITSCHEWSKAJA and R. FINKELSTEIN, Beitr. z. Klin. d. Tuberk. **68**:336, 1928.

Although none of these three procedures is diagnostic of tuberculosis, they help to understand the prognosis of a given case. The sedimentation and Matéfy

reactions indicate the degree of activity. The Arneth count indicates the amount of disturbance in the balance of the body. All three procedures are of value only if repeatedly applied.

MAX PINNER.

MORPHOLOGIC BLOOD STUDIES IN PULMONARY TUBERCULOSIS. K. STEUDTNER, Beitr. z. Klin. d. Tuberk. **68**:353, 1928.

In 500 patients, the morphologic blood picture was studied in serial examinations. The author believes that such studies are prognostically important, and give reliable indication for the success or failure of therapeutic procedures.

MAX PINNER.

COMPARATIVE STUDIES ON BASAL METABOLIC RATE AND SEDIMENTATION REACTION IN TUBERCULOUS PATIENTS AT LOW AND HIGH ALTITUDES. H. KAPP, Beitr. z. Klin. d. Tuberk. **68**:378, 1928.

The basal metabolic rate was, in average, lower in high altitudes (Davos). The sedimentation rate was lower. The period during which respiration could be interrupted was decreased. These studies would indicate that the climatic therapy in high altitudes does not act by stimulation but by relative rest.

MAX PINNER.

COSTA'S REACTION IN TUBERCULOSIS OF THE BONES AND JOINTS. M. M. ALTSCHULER, Beitr. z. Klin. d. Tuberk. **68**:399, 1928.

On the basis of tests on 125 patients with tuberculosis of the bones and joints, the following conclusions were drawn: Costa's reaction is not specific for tuberculosis. Moderately severe and severe cases have usually a rather strong reaction which at times precedes grave clinical manifestations.

MAX PINNER.

DIRECT ISOLATION OF TUBERCLE BACILLI FROM THE BLOOD STREAM. K. BINGOLD, Beitr. z. Klin. d. Tuberk. **68**:734, 1928.

The blood is received in 15 or 20 per cent gelatin. The erythrocytes settle down, and are then transferred on egg mediums, in the special container described in a report from Much's Institute. With this technic, three positive cultures were obtained from ten samples.

MAX PINNER.

SO-CALLED SPONTANEOUS ENCEPHALITIS OF RABBITS. H. PETTE, Ztschr. f. Hyg. u. Infektionskr. **108**:700, 1928.

Rabbits, the spinal fluid of which had been tested for the absence of any meningeal irritation, were inoculated in the testicle with brain material from twelve cases of paresis. A positive result was obtained five times. The animals with a positive reaction developed, from three to eleven weeks after the inoculation, signs of a meningo-encephalitis, as shown by an increased cell count in the cerebrospinal fluid. The clinical manifestations were slight. The histologic changes, however, were characteristic. The same result was obtained four times in seven cases by the intratesticular inoculation of fresh syphilitic material from other sources. Meningo-encephalitis developed in three of eleven rabbits after the cisternal injection of cerebrospinal fluid from cases of epidemic encephalitis. The same clinical and histologic changes were also observed in a group of animals that had not been treated. The spontaneous disease occurred in epidemic form in the spring of 1925, later only sporadically. The disease in all cases could be transmitted to healthy rabbits. Of twenty-seven controls inoculated with material from various other sources, only one became encephalitic; this occurred four months after the inoculation. The encephalitis of rabbits is characterized by a perivascular meningeal round cell infiltration of varying degree and the appearance

of granulomatous nodules which sometimes have a necrotic center. Foci of round cell infiltration are also found in the liver and the kidneys.

Pette believes that the disease was identical in all cases and was induced by a protozoon-like organism which has been described by many previous investigators. He actually demonstrated the presence of these microbes only in a relatively small number of his animals, but he found them both when the disease had been acquired spontaneously and when it had been acquired by inoculation. He is inclined to think that this peculiar virus is widely disseminated and is harbored by many animals as a harmless parasite. It assumes pathogenic properties under cetain favorable circumstances which may be of exogenic or endogenic origin. This seems to occur particularly when the animals are inoculated with material containing a neurotropic virus such as the encephalitis virus or *Spirochaeta pallida*.

W. Ophüls.

Anthrax Studies. E. Singer, Ztschr. f. Immunitätsforsch. u. exper. Therap. **54**:144, 1927.

The residual nitrogen content of the liver and spleen in guinea-pigs infected with anthrax is increased up to four times the normal value. In muscle tissue, the observations are approximately normal. The blood sugar rises during the infection, in many cases falling during the agonal stage. The electrocardiograms of two rabbits infected with the anthrax bacillus were normal.

Paul R. Cannon.

The Lysozyme Effects of Egg-White. T. Kigasawa, Ztschr. f. Immunitätsforsch. u. exper. Therap. **54**:155, 1927.

Lysozyme is a substance occurring in plant and animal tissues which has a bacteriolytic effect on many bacteria, particularly gram-positive ones. The substance is more thermostable than bacteriolysins, but may be destroyed by high temperatures. The dissolving effect is quantitative, and under proper conditions all of the lysozyme may be used up in the reaction. Free alkali inhibits lysozyme action but does not completely eliminate it. The lysozyme also makes bacteria sensitive to changes in p_H.

Paul R. Cannon.

The Prognostic Value of Examination of the Sputum, the Sedimentation Reaction of Erythrocytes and the Gerlocy Plasma Lability Reaction in Pulmonary Tuberculosis. J. Von Szaboky, Ztschr. f. Tuberk. **50**:413, 1928.

Examinations of the sputum yield prognostically important information only in serial studies. An increasing number of bacilli indicate usually progressive disease. Decreasing numbers indicate a benign course. The presence of Much's granules is a prognostically favorable sign. The prognostic significance of long and short bacilli is uncertain. Gerlocy's reaction is prognostically significant. A negative reaction excludes the possibility of active pulmonary tuberculosis. The strength of the reaction is indicative of the activity and of the pathologic-anatomic character of the lesion. The sedimentation reaction is less reliable in every respect.

Max Pinner.

The Uric Acid Content in Healthy and in Tuberculous Patients in High Altitudes. P. Borchhardt, Ztschr. f. Tuberk. **50**:473, 1928.

In normal persons in high altitudes, the amount of uric acid in the blood is significantly smaller than it is at lower levels. During the period immediately preceding a febrile disease or a tuberculous exacerbation, the amount of uric acid increases considerably; it decreases rapidly during periods of high temperature. Afebrile or subfebrile tuberculous patients have high normal or slightly supranormal values. Normal values are found consistently in patients whose lesions continued to heal.

Max Pinner.

Immunology

IMMUNITY IN LOBAR PNEUMONIA. R. L. CECIL, D. R. RHOADES and W. D. SUTLIFF, J. Clin. Investigation **6**:22, 1928.

The pneumococcidal power of whole blood was expressed as the number of pneumococci killed by 0.5 cc. of blood in twenty-four hours. Heparin was used as an anticoagulant. In patients with minor complaints and no history of pneumonia the range was from 0 to 10,000, while in patients convalescing from lobar pneumonia, there was an increase to from 100,000 to 10,000,000. In lobar pneumonia the pneumococcidal power of the blood was normal or below in the acute stage, rising about the time of crisis and reaching its highest point after the crisis. When bacteremia was present before the crisis, no pneumococcidal power was present, although in one patient with acute pneumococcal endocarditis there was simultaneous bacteremia and high degree of pneumococcidal power. Immunity in patients with pneumonia with normal or subnormal pneumococcidal power, was increased by giving Felton's antipneumococcus serum.

THE USE OF TRYPAN BLUE TO DEMONSTRATE THE IMMEDIATE SKIN REACTION IN RABBITS AND GUINEA-PIGS. SUSAN GRIFFITH RAMSDELL, J. Immunol. **15**:305, 1928.

By the intravenous administration of trypan blue, the immediate skin reaction to a homologous antigen may be demonstrated in serum treated rabbits and guinea-pigs in the usual testing for direct, passive and reversed passive sensitization in both animals. The same type of reaction may be shown to an injection of serums of sensitized animals, of serums showing so-called primary toxicity for the guinea-pig, and to high dilutions of histamine. It is believed that the infiltration of the dye into these reaction sites is, at present, to be looked on as no more than a sort of indicator of the presence of an edematous change which is an expression of a toxic action on the capillary endothelium.

AUTHOR'S SUMMARY.

THE PRESERVATION OF ALEXIN IN CARBON DIOXIDE. GEORGE VALLEY and JAMES G. MCALPINE, J. Immunol. **15**:313, 1928. GEORGE VALLEY, Ibid. **15**:325, 1928.

Of the various gases employed in our experiments carbon dioxide alone exerted a pronounced preservative action on serum alexin. When enclosed in a carbon dioxide atmosphere in an airtight container, the alexin may be preserved for reasonable periods of time (three to five weeks) without any loss of potency. Under experimental conditions it has been kept for several months without deterioration. Alexin preserved in carbon dioxide has been found to be satisfactory in the routine alexin fixation test for infectious abortion in cattle. The method proposed is easily employed, involving no exact or complicated analytic procedures. A simple downward displacement of atmospheric air with carbon dioxide gas and the closing of the container are the only additional manipulations required in handling the alexin. In all likelihood the preservative action of carbon dioxide is due to establishing conditions that favor reduction and prevent oxidation.

OPHTHALMIC TEST FOR SENSITIVENESS TO HORSE SERUM. SOPHIE SPICER, J. Immunol. **15**:335, 1928.

The ophthalmic test appears to be safe. Undiluted serum or serum diluted 1:1 or 1:2 can be used. The reactions generally appeared in from ten to fifteen minutes after the application of the serum and cleared up within from one-half hour to two hours. All the patients who gave positive ophthalmic tests gave positive intradermal reactions.

ULTRAMICROSCOPIC FINDINGS IN THE SERUM OF THE ANAPHYLACTIC GUINEA-PIG. SUSAN GRIFFITH RAMSDELL and CLARA C. KAST, J. Immunol. **15**:343, 1928.

Using the ultramicroscope in a study of the serum of the sensitized guinea-pig, we have found the flocculation phenomenon, as postulated by Kopaczewski, to occur irregularly, to appear to be simply a weak precipitin reaction, and to have no constant relation to the capacity of the animal to show shock. Certain changes in the appearance of the serums were often noted following shock, but the nature of these were not resolvable by the use of the technic as outlined.

AUTHORS' SUMMARY.

PARENTERAL DENATURIZATION OF FOREIGN PROTEINS IN IMMUNE DOGS. W. H. MANWARING, H. D. MARINO, J. L. AZEVEDO and H. C. TORBERT, J. Immunol. **15**:351, 1928.

The rate of parenteral denaturization of horse proteins in dogs immune to horse serum, therefore, is distinctly slower than the rate in normal dogs. There is not the rapid denaturization previously observed in hypersensitive dogs, all tests with hypersensitive donors being negative after the eighteenth hour. Nor is there the still more rapid denaturization one would predict from the unitarian conception of the relation of anaphylaxis to immunity. The biochemical properties or relationships responsible for rapid protein denaturization in hypersensitive dogs are apparently wholly absent or inoperative in immune dogs. This observation is consistent with our previous conclusion of the nonidentity of specific antibodies in hypersensitive and immune dogs.

AUTHORS' SUMMARY.

PHYSICO-CHEMICAL RELATIONSHIPS IN ANAPHYLAXIS. F. R. VAN DE CARR, W. R. LYONS and O. B. WILLIAMS, J. Immunol. **15**:355, 1928.

Heparin, even when given in amounts sufficient to render the blood incoagulable for seventy-two hours, will not prevent or alleviate the anaphylactic syndrome in guinea-pigs when the colloidal balance of the blood has been disturbed by the previous injection of heterophile antigen. Anaphylactic shock, ranging in intensity from slight transitory symptoms to fatal termination, can be elicited in guinea-pigs hypersensitive to casein by the intracardial injection of properly graded doses of highly purified casein. The colloidal dispersion of the blood may be altered by the intracardial injection of suitable amounts of heterophile antigen or 2 per cent sodium citrate. The clotting time, as determined by the capillary tube method, of the blood of guinea-pigs inoculated intracardially with 2 per cent sodium citrate, is materially lowered. Both heterophile antigen and 2 per cent sodium citrate when injected intracardially into sensitized guinea-pigs, alter the colloidal state of the blood sufficiently to cause fatal results from a dose of antigen (casein) that would normally elicit only mild transitory symptoms.

AUTHORS' SUMMARY.

THE SUSCEPTIBILITY OF ESKIMOS TO AN EXTRACT FROM TOXICODENDRON RADICANS (L). PETER HEINBECKER, J. Immunol. **15**:365, 1928.

The Baffin Island Eskimo is not susceptible to the active principle of *Toxicodendron radicans* (L). This lack of susceptibility is considered to be due to a lack of contact, rather than to a lack of any racial characteristics essential to the development of susceptibility.

AUTHOR'S SUMMARY.

THE EFFECTS OF PERFUSION UPON THE ANTIBODY CONTENT OF SERUM AND ORGANS. JULES FREUND and CAROLINE E. WHITNEY, J. Immunol. **15**:369, 1928.

Agglutinins of the isolated liver of actively or passively immunized rabbits can be removed by perfusion. Perfusion of the living rabbit can remove more

agglutinins from the rabbit than the blood contained at the beginning of the perfusion. Perfusion of the living rabbit reduces the antibody content of the liver and spleen considerably and fairly parallel with the reduction of the agglutinin content of the blood. This suggests that just as the antibodies penetrate from the blood into the liver and spleen rapidly, as found in a previous study, they enter from the liver and spleen into the blood stream rapidly. Perfusion of the living rabbit does not remove the agglutinin content of the uterus and skin. The state of perfusion-fastness probably does not depend on an attachment of antibodies to the cells of the organs.

AUTHORS' SUMMARY.

EFFECT OF LOW TEMPERATURES ON DIPHTHERIA TOXIN-ANTITOXIN. ELLIOTT S. ROBINSON AND BENJAMIN WHITE, J. Immunol. **15**:381, 1928.

Enough evidence is available to justify the statement that under certain conditions some toxin-antitoxin mixtures will become toxic when frozen. These conditions are, so far as they have been determined, the persistence of low temperatures, during more than a minium period, on toxin-antitoxin mixtures of certain concentrations, containing phenol or tricresol, and possessing other as yet undetermined characteristics. To this should be added the possibility that the phenomenon is in part if not entirely one of dissociation of toxin and antitoxin and only in part, if at all, one of destruction of antitoxin.

AUTHORS' SUMMARY.

HYPERSENSITIVENESS TO HELMINTH PROTEINS. FRANCES A. COVENTRY and WILLIAM H. TALIAFERRO, J. Prev. Med. **2**:273, 1928.

Hypersensitiveness to *Ascaris* protein was manifest in 80 per cent of 130 Honduranean patients tested by the scratch method, as shown by wheal formation and erythema within twenty minutes after testing. This sensitiveness could not be correlated with the presence of *Ascaris* infection, nor with the presence of other helminths. The test, therefore, has no diagnostic significance. Precipitin tests with *Ascaris* extracts, positive in 61 per cent of the ninety cases studied, could not be correlated with the presence of *Ascaris* in the stools nor with the presence of other infections. No relation between skin reactivity and presence of precipitins in the blood could be demonstrated. Wheal formation and erythema followed the scratch test with hookworm extracts in 80 per cent of eighty-four patients tested, but no correlation existed between the reactions and presence or absence of infection. Wheal formation and erythema followed the scratch test with *Trichuris* extracts in 25 per cent of sixty-four cases studied. Here again, no relation was found between positive tests and the presence of infection.

AUTHORS' SUMMARY.

PREVENTION OF DIPHTHERIA AND SCARLET FEVER IN NURSES. LUDVIG HEKTOEN and CHARLOTTE JOHNSON, J. Prev. Med. **2**:289, 1928.

Student nurses who give negative reactions to the Schick and Dick tests appear to be well protected against diphtheria or scarlet fever. Susceptible nurses who are immunized before entering on active service in caring for patients with diphtheria or scarlet fever also appear to be well protected. By means of the Schick and Dick tests followed, when necessary, with active immunization, nurses can be selected who are practically free from the danger of diphtheria and scarlet fever.

AUTHORS' SUMMARY.

THE PROTECTIVE ACTION OF SERUM AGAINST HEMOLYSIN IN DIPHTHERIA. J. GORDON and J. SCIENCE, Quart. J. Med. **21**:345, 1928.

In diphtheria the protective power of the serum against a hemolysin is markedly diminished, this protective power returning in simple uncomplicated cases by the end of the third week. In most cases of paralysis the diminished protective power

lasts for a considerable time. In a few cases of paralysis there will be no interference with protective power of the serum. In fatal cases there is a marked loss of the protective power. The protection of the serum against hemolysin should be estimated early in the disease as an indication of the amount of toxin present in the blood, in order to find some index to the amount of antitoxin to be injected and at various periods of the disease in order to assess the prognosis and the possible development of paralysis.

N. ENZER.

BLOOD GROUPS OF MOTHER AND CHILD. R. DEBRÉ and M. HAMBURGER, Rev. franç. de pédiat. **4**:127, 1928.

In a study of the blood groups of more than 100 new-born infants and infants a few days, weeks, or months old, Debré and Hamburger found that: 1. The blood group of young infants could be defined exactly, even with blood taken from the umbilical cord. 2. Blood group examination performed on the same infant several weeks or months after the first examination always gave the same result. 3. In only 60 per cent of the cases did blood from the infant belong to the same group as blood from the mother. Therefore, no matter who is the donor and no matter what is the age of the recipient, tests for the compatibility of the two bloods should always be made before performing a transfusion.

ISOHEMAGGLUTINATIVE GROUPS IN HORSES. A. P. NEWODOW, Abstr. in Ukrainisches Zentralbl. f. Blutgruppenforsch. **2**:72, 1928.

According to the isohemagglutinative reactions with their serum and corpuscles 1,730 horses were classified in groups corresponding to those for human blood as follows: 0.30 per cent; A, 18 per cent; B, 18 per cent, and AB, 36 per cent. About from 4 to 6 per cent of the whole number failed to correspond to any group, and subgroups probably exist. The grouping of 500 horses, included in the 1,730, that had been treated with mallein was somewhat different: 0.6 per cent; A, 19 per cent; B, 8 per cent, and AB, 67 per cent. The agglutinative power of group B is weak, especially for group A cells and a decrease of agglutinative titer occurs in all groups chiefly in the winter. In from 8 to 10 per cent of these tests autoagglutination appeared almost exclusively in group O.

INTRACUTANEOUS INJECTIONS OF SWEAT IN TUBERCULOSIS. E. DORN, Ztschr. f. Tuberk. **51**:134, 1928.

The sweat of tuberculous patients contains antigenic substances as does the urine. On the basis of this fact, a method was elaborated to demonstrate these antigenic substances by intracutaneous injection, in accordance with the work of Wildbolz in his auto-urinary test. Of 171 tests, 81.3 per cent were according to theoretical expectations. This test is unreliable in the diagnosis of incipient tuberculosis.

MAX PINNER.

PREMONITORY SERUM REACTIONS IN SOLDIERS APPARENTLY FREE OF TUBERCULOSIS. W. E. HILGERS and SACHS-MÜKE, Ztschr. f. Tuberk. **51**:468, 1928.

There is apparently a relation between positive Besredka reactions and the presence of tuberculous foci demonstrated by x-ray studies. The serologic tests may still be positive a long time after a lesion has become quiescent. No positive reactions were obtained shortly before a reactivation of a tuberculous focus, or shortly before the beginning of an active tuberculous process. Besredka's reaction helps to confirm a diagnosis, but is not instrumental in demonstrating the early inception of the disease.

MAX PINNER.

Tumors

BASAL SQUAMOUS CELL EPITHELIOMA. HAMILTON MONTGOMERY, Arch. Dermat. & Syph. **18**:50, 1928.

Basal cell epithelioma is not morphologically a closed entity. It may become, through metamorphosis, a basal squamous cell epithelioma or even a squamous cell epithelioma. Transitional epitheliomas, presenting features of both basal cell and squamous cell epithelioma, occurred in 12.6 per cent of a series of 119 cases of epithelioma of the skin, and were classified as basal squamous cell epithelioma. They represented a metamorphosis of basal cell epithelioma to squamous cell epithelioma and were not degenerative forms of the latter.

In a series of basal cell epitheliomas diagnosed clinically as such, from 15 to 20 per cent on microscopic examination will probably prove to be transitional in character. The microscopic picture of basal squamous cell epithelioma is characteristic and diagnostic, but may be confused with a malignant squamous cell epithelioma, grades 3 or 4, unless a thin, well stained section is studied carefully. The development of basal squamous cell epithelioma from the epidermis is shown. Roentgen therapy does not, as a rule, cause basal squamous cell epithelioma, although it may be a factor in increasing the malignancy of a tumor. In 60 per cent of the cases these transitional epitheliomas are indistinguishable clinically from basal cell epitheliomas, the distribution and course of which they tend to approximate. A positive diagnosis can be made only by microscopic examination. The dangers of biopsy have been overemphasized in the past. Basal squamous cell epithelioma may occasionally metastasize in the same form for years, or it may metastasize as a squamous cell epithelioma. Most, if not all, cases of so-called metastatic basal cell epithelioma on microscopic examination will prove to be basal squamous cell or squamous cell epithelioma. Basal squamous cell epithelioma, in the majority of cases, is relatively resistant to roentgen and radium treatment as compared with basal cell epithelioma. Radiotherapy should be used only as a last resort. Surgical treatment, with an unusually wide excision because of the insidious infiltration of the tumor cells, is indicated whenever possible. The prognosis in these cases of transitional tumor must be guarded. They correspond to the more malignant of the squamous cell epitheliomas of grade 2. The epitheliomas tend to recur. Five years should elapse without recurrence before a cure is pronounced.

AUTHOR'S SUMMARY.

MULTIPLE MYELOMA. C. F. GESCHICKTER and M. M. COPELAND, Arch. Surg. **16**:807, 1928.

In a lengthy article, supplemented by a fairly complete bibliography, 425 cases are reviewed, 80 per cent of which occurred from the fourth to the seventh decade of life; only five patients were less than 35 years of age. The disease is twice as common among males as females, and forms 0.03 per cent of all types of malignancy. Of 400 cases of tumor of the bone in the Johns Hopkins Hospital records, 3 per cent were multiple myeloma; trauma is mentioned in the history of 20 per cent. Pain was found to be an outstanding symptom; in 70 per cent of the cases it was lumbar and sacral; in 20 per cent, in the chest, and in 10 per cent, elsewhere. The pain is described as rheumatic, but girdling and neuritic pains were common. There were periods of relative relief with acute exacerbations and progressive neurologic manifestations. The multiplicity of the tumors is the noteworthy feature. In 90 per cent, the ribs sternum clavicles and spine were involved; and in 40 per cent the skull, pelvis and extremities. This series of cases did not include any in which the extremities alone were affected.

The tumors may vary in size from that of a pinpoint to that of an orange. They are usually tender and painful, and often are recognized as the result of a pathologic fracture, many of them later causing a crackling sensation on palpation. The tumors may decrease in size, apparently spontaneously. In 60 per cent of the cases thoracic deformity occurred, and a so-called parasternal rosary was

present in 50 per cent. Flattening of the lumbar curve, dorsal kyphosis and collapse of the vertebrae developed in the vertebral column. The frequency of pathologic fractures has been recognized. In the cases at Johns Hopkins Hospital, 50 per cent of such fractures occurred in the ribs and clavicle. About 60 per cent of all pathologic fractures were found to be due to multiple myeloma; frequently there were multiple fractures.

The lungs showed chronic bronchitis and emphysema with pleurisy in about 55 per cent of the cases, and subpleural nodules were common. Paraplegia developed in 40 per cent from compression of the spinal cord. Chronic nephritis developed in 70 per cent, and gastro-intestinal changes were found to occur chiefly as terminal complications. The occurrence of gastric ulcers was interesting, especially in view of the fact that metastases to the stomach and duodenum were found. The spleen, liver, thyroid, suprarenals, ovaries, meninges and lymph nodes occasionally showed metastases, but pulmonary metastases were rare. Bence-Jones protein was found in the urine in 65 per cent of the patients, but this protein occurred in 27 per cent of the patients with other conditions of the bone and marrow. The condition of the blood was not constant. Anemia of primary and secondary types occurred, with and without leukopenia, but aplasia was not found.

The roentgen examination is extremely important in the diagnosis. The tumors show up as rounded, punched-out areas. Occasionally, however, diffluent areas result, so that the bone appears to be rarefied and mottled. The microscopic examination of the tumor is, of course, the last resort in the diagnosis. The tumor is generally surrounded by a thin layer of bone. It bleeds easily, and is usually dark red and gelatinous. The majority of the cells are round and oval shaped, with eccentrically placed nuclei; occasionally, multinucleated cells are present. These cells have been described frequently as plasma cells, but they do not take the typical stain, and the perinuclear halo is lacking. Intermingled with these cells is a much smaller cell closely resembling a lymphocyte. Occasionally myeloblastic or myelocytic types occur, but all workers agree on the differentiation of these types from that just described. Only in rare instances do these cells enter the circulation as in the leukemias.

The initial diagnosis of this disease early in the condition occasionally is difficult. Certain things, however, are outstanding, namely, the skeletal changes described, the characteristic backache and radiating pains, and, in many instances, the anemia, the Bence-Jones protein in the urine and chronic nephritis. The disease pursues a progressively downhill course lasting about two years after the date of recognition.

N. ENZER.

THE PRIMARY SITUATION OF ONE HUNDRED AND THIRTY-THREE SPONTANEOUS TUMORS IN THE LOWER ANIMALS. WILLIAM H. FELDMAN, J. Cancer Research **11**:436, 1927.

Feldman noticed that the eye of cattle and horses showed the greatest predilection for carcinoma. In the horse the penis was the next most common site for carcinoma; in cattle the same organ was attacked by fibroblastic tumors. Internal neoplasms in cattle often originated in the suprarenal gland. In the hog, he frequently noticed an embryonal tumor of the renal gland, the melanosarcoma of the skin being the most common type. The dog is probably susceptible to all of the common neoplastic diseases. Carcinoma, however, was rarely found in the dog.

B. M. FRIED.

POSTOPERATIVE ENDOMETRIOMA OF THE ANTERIOR ABDOMINAL WALL. EHRENPREIS and RAYMOND LETULLE, Bull. de l'Assoc. franç. p. l'étude du cancer **17**:19, 1928.

The authors report a case of an endometrioma in a woman, aged 31. The new growth developed in the round ligaments which previously were attached by the surgeon to the anterior abdominal wall. The tumor had a glandular structure

which showed all the characteristics of the uterine mucosa. There was considerable cystic degeneration and inflammation which apparently caused the severe pain in the region of the new formation. The growth was extensive but did not show any malignant features.

B. M. FRIED.

LYMPHOSARCOMA OF THE RECTUM: CURE LASTING SIX YEARS EFFECTED BY RADIO AND CURITHERAPY. STOLZ, GUNSETT and OBERLING, Bull. de l'Assoc. franç. p. l'étude du cancer **17**:63, 1928.

A lymphocytoma of the rectum, under the influence of radium therapy, did not recur for six years.

B. M. FRIED.

A DIFFUSE SCAPULO-CERVICAL FIBROMA SUCCESSFULLY TREATED. GUNSETT and OBERLING, Bull. de l'Assoc. franç. p. l'étude du cancer **17**:67, 1928.

A tumor which was found in a woman, aged 26, was diagnosed as a "fasciculated fibroma." Oberling who investigated the tumor stated that in spite of its histologic benignity it often metastasizes and grows with rapidity. In a number of instances it was shown to be remarkably sensitive to radium. Radium was applied four successive times within one and a half years.

B. M. FRIED.

THE INFLUENCE OF ROENTGEN RAYS AND RADIUM ON PRIMARY CANCERS OF THE LUNGS. S. LABORDE and R. HUGUENIN, Bull. de l'Assoc. franç. p. l'étude du cancer **17**:74, 1928.

Two of four cases of primary carcinoma of the lungs occurred in men, aged 27 and 22 years, respectively, one in a boy, aged 12 years, and one in a man, aged 47. As in cancer of other tissues, the sensitiveness of the tumor to roentgen rays and radium depends apparently on the histologic structure of the new growth. Thus, large celled, nonkeratinizing tumors are influenced by this treatment whereas "round cell' tumors are resistant. The authors, however, are conservative in the evaluation of this method of treatment of pulmonary cancers; they state that it leads to the considerable amelioration of symptoms. The history and histologic condition of four cases are given.

B. M. FRIED.

MYO-SCHWANNOMA OF THE GASTRIC FUNDUS. ABADIE and ARGUAD, Bull. de l'Assoc. franç. p. l'étude du cancer **17**:104, 1928.

A number of French surgeons and pathologists noted previously that tumors of the stomach reported as sarcomas are often only benign growths originating from the sheath of Schwann; these were designated as schwannomas. In the case described by Abadie and Arguad, the new growth occurred in a man, aged 55, who on examination showed a hard and movable tumor in the region of the lesser curvature of the stomach, confirmed by roentgen examination. The growth when removed proved to be the size of a small orange; it was lobulated and covered with a slightly altered mucosa. The histologic examination showed "a proliferation of a syncytium of Schwann either diffuse or as a fibroglioma having delicate anastomosing fibrils. The nuclei were arranged en pallissade, and there was a microcystic degeneration of the syncytium of Schwann."

B. M. FRIED.

CANCER AND DISTURBANCES IN THE METABOLISM OF SUGARS. E. JOLTRAIN, T. REVEZ and R. WOLFF, Bull. de l'Assoc. franç. p. l'étude du cancer **17**:125, 1928.

Warburg produced evidence to show that the metabolism of a carcinomatous cell is essentially different from that of a normal somatic cell. Whereas the life energy of the normal cell is maintained by the absorption of oxygen, that of a neoplastic cell is carried on by "lactic fermentation" without the utilization

of oxygen from the air. In other words, normal cells burn dextrose to form carbon dioxide and water, while tumor cells transform dextrose into lactic acid. In this way cancerous tissue resembles embryonic tissue; the difference is only that in embryonic tissue the fermentation disappears in the presence of oxygen, whereas in the cancerous cells both processes occur simultaneously. The metabolism of yeast is identical with that of carcinomatous cells.

The peculiarities of sugar metabolism in cancer has been the object of numerous investigations. The regulation of dextrose in this disease has been studied by the sugar tolerance tests, by the determination of the respiratory quotient and by the basal metabolism.

Joltrain and his associates studied twelve patients with cancer of the uterus, stomach, breast and rectum. They found that following the ingestion of sugar the respiratory quotient in these patients either remained stationary, or raised slightly, the average increase being about 7 per cent, and in the normal controls, 16 per cent. They concluded, therefore, that there was a disturbance in carbohydrate metabolism in patients with cancer. Since the metabolism in carbohydrates is regulated by the endocrine glands, there would appear to be a connection between the development of cancer and the disturbance of the glands of internal secretion.

B. M. FRIED.

CELLS OF KULTSCHITZKY IN A CYLINDRIC GASTRIC EPITHELIOMA AND ITS METASTASES. PIERRE MASSON and JOSEPH F. MARTIN, Bull. de l'Assoc. franç. p. l'étude du cancer **17**:139, 1928.

The cells of Kultschitzky are present in the intestinal mucosa of vertebrates and mammalians. They are triangular or bottle-shaped and contain, in their cytoplasm, chromaffin granules which are likewise argentophile. Kultschitzky believed that they were leukocytes which were aiding in the absorption of nutritive substances; other writers thought that they represented an integral part of the intestine. There was also a disagreement as to the origin of the cells. Masson and Martin, in a study of a case of cancer of the gastric ulcer type with metastases to both ovaries (Krukenberg's tumor), found the cells in question in the primary and in the ovarian new growths. This fact, in their opinion, strengthened the conception that the cells were of intestinal origin.

B. M. FRIED.

RETICULOSARCOMA AND RETICULOENDOTHELIOMA OF THE BONE MARROW (EWING'S SARCOMA). CHARLES OBERLING, Bull. de l'Assoc. franç. p. l'étude du cancer **17**:259, 1928.

In an excellent discussion, illustrated by seven clinicopathologic reports, Oberling produces evidence that Ewing's sarcoma "really exists, and that this variety of tumor represents an anatomical and clinical entity."

B. M. FRIED.

A CASE OF PAGET'S DISEASE IN THE ARMPIT WITH CANCER. A. CIVATTE, Bull. de l'Assoc. franç. p. l'étude du cancer **17**:297, 1928.

Paget's disease is regarded as a precancerous condition of the nipple, susceptible to development into a cancer. When a cancer occurs, its exact origin is not always easy to trace. While Paget himself thought that the disease always started in the epidermis, more recent investigations indicate that the malignant condition originates in the glandular structures beneath the skin. There is also a disagreement as to the nature of the peculiar clear cells (Paget's cells) found in the tissues. By one author they are interpreted as cancerous cells which have migrated toward the epidermis from underneath; by others they are classified as cells of the malpighian layer. Civatte reports an interesting case of an extramammary Paget's disease. In this case the malady developed before cancerization of the glands.

The author is of the opinion that Paget's cells originate in situ. He states that the disease leads not only to a glandular cancer, but also to "cutaneous"

cancers which closely resemble that of a nevus carcinoma. In certain instances, both varieties of cancer may be combined in the same tumor. Cancers which follow Paget's disease are sensitive to the roentgen ray.

B. M. FRIED.

CANCER FROM INCLUSION OF HUMAN BILIARY CALCULI IN THE GALL BLADDER OF THE GUINEA-PIG. PIERRE DELBERT and HENRI GODARD, Bull. de l'Assoc. franç. p. l'étude du cancer **17**:347, 1928.

By inserting foreign bodies into the gallbladder of thirty guinea-pigs, Kazama noticed that four developed cancer of this organ with metastases to the thorax, intestines and liver. He thought, therefore, that the gallbladder of the guinea-pig was an elective organ for the study of experimental cancer. Leitch in similar experiments confirmed the observations made by Kazama. Lazarus-Barlow claimed that calculi from a cancerous gallbladder are radioactive and that this activity led to the development of cancer. By the insertion of stones from a cancerous gallbladder in man into the gallbladder of the guinea-pig, Delbet and Godard did not produce an epithelial malignant disease in the biliary vesicle of guinea-pigs. They could not confirm the observation that stones from cancerous gallbladders are radioactive.

B. M. FRIED.

A LYMPHOBLASTIC SARCOMA OF THE STOMACH: CURE LASTING FIVE YEARS EFFECTED BY ROENTGEN RAYS. GUNSET and OBERLING, Bull. de l'Assoc. franç. p. l'étude du cancer **17**:385, 1928.

Gunset and Oberling report an interesting case of a gastric lymphosarcoma found at a laparotomy and treated with roentgen rays. Five years after the operation the patient was still in good health.

B. M. FRIED.

THE PROGNOSIS OF INTRA-OCULAR MALIGNANT TUMORS, HILJA TERÄSKELL, Acta Ophth. **6**:110, 1928.

Teräskeli studied fifty-five cases of intra-ocular tumors. Forty-six of these, including twenty-six uveal sarcomas, nineteen gliomas and one metastatic carcinoma, were seen from 1912 to 1925, a period of thirteen years, at the Helsingfors University Eye Clinic; nine cases were from private practice. Twenty-one of the thirty-three cases of uveal sarcoma occurred in men; the greatest number, between the ages of 30 and 70. These tumors were divided according to four stages: (1) nonstimulating (12 cases); (2) glaucomatous (11 cases); (3) extrabulbar extension (6 cases); (4) general metastases. The greatest number were diagnosed in the third stage. Enucleation was performed in most instances. Thirty-one were in the choroid, and two in the corpus ciliare. Round and spindle cells predominated. The pigment was variable. The variation in histologic structure did not appear to have any effect on the prognosis. Not all were operated on. Thirteen of the eighteen listed were regarded as cured; four developed metastases. Most of the twenty-one cases of glioma (13 female and 8 male) occurred before the age of 5 years; nine were in the right eye, seven in the left, and in five or 23.8 per cent both eyes were involved. Twenty-two of the eyes were enucleated. Of the thirteen cases tabulated, ten (62.5 per cent) recovered and three (37.5 per cent) died. Metastases in the fatal cases were local in the brain or in neighboring bones.

F. R. MENNE.

EFFECT OF IRRADIATION ON TISSUE CULTURES. L. SANTESSON, Upsala Läkaref. Förh. **34**:591, 1928.

In Santesson's nine series of chicken fibroblast cultures, at least 40 days old, roentgen irradiation caused a definite arrest in growth in all cases after transfer, the more marked the higher the dose, and most marked in the second culture period. In experiments with Peyton Rous' chicken sarcoma the effect was most

marked in the fourth or fifth passage, the more marked the greater the dose, but in all the series these cultures could be carried farther (now six months). There was a definite latent period both in fibroblast and in sarcoma cultures. No certain stimulating effect was seen. This is a preliminary report.

GENESIS OF TUMORS AND ALLIED FORMATIONS. W. BOSAEUS, Upsala Läkaref. Förh. **34**:603, 1928.

In this first part of Bosæus' work on the possible relation of reproduction to tumor formation in vertebrates, he deals with the authentic cases of self-fertilization and parthenogenesis in fishes and amphibia and with formations discovered in all vertebrates. He describes the results of pathologic parthenogenesis due to parthenogenetic development induced experimentally in ova of certain amphibia, with development of the resulting embryos in their own mother organisms.

Medicolegal Pathology

ILL EFFECTS FROM LUMBAR PUNCTURE. L. M. WIEDER, Am. J. M. Sc. **173**:854, 1927.

Presumably only a few of the mishaps following lumbar puncture have been reported. About five years before, the deaths numbered more than seventy. There has usually been a considerable increase of intracranial pressure from disease within the cranium, and among such diseases tumor and apoplexy are especially common. Herniation of the brain stem into the foramen magnum and acute cerebral edema are perhaps more commonly given as reasons for death; meningitis due to infection through the wound made and prolonged oozing of spinal fluid are mentioned.

The death reported by Wieder evidently followed prolonged drainage of the fluid through the wound of the dura into the tissues about the lumbar part of the spine. The infiltration is described as massive. Pronounced syphilitic encephalomyelitis was present. This was the second death occurring among 27,000 lumbar punctures performed during fifteen years in the department of dermatology and syphilology of the University of Michigan. The other death was caused by meningitis.

E. R. LE COUNT.

DEATH FROM ALYPIN POISONING. A. RILEY, New England J. Med. **199**:267, 1928.

Alypin N.N.R., the hydrochloride of 2-benzoxy-2-dimethyl-aminomethyl-1-dimethylaminobutane, presumably equal to cocaine in its local anesthetic effects but not mydriatic, is herein presented in a distinctly toxic rôle. In a man, aged 35, whose symptoms warranted cystoscopy, a sound was passed one morning. The next morning 1 drachm (3.75 cc.) of 4 per cent alypin was injected into the urethra; this was followed by brief massage and then the excess of the solution was allowed to run out. Before cystoscopy could be performed, convulsions set in and respiration ceased. Intravenous injections of epinephrine and artificial respiration were administered, and in five minutes the heart began to beat. After one hour the patient breathed. He remained unconscious for forty-eight hours and then died. The author has used alypin as a routine for six years and has seen toxic symptoms only in persons in whom the urethra has been previously traumatized.

GEORGE RUKSTINAT.

THE TREND OF MODERN LEGISLATION AND THE MEDICOLEGAL WORK OF THE PRACTITIONER. JOHN GLAISTER, Glasgow M. J. **109** and **110**:1, 1928.

These articles deal in an interesting way with the medicolegal work of the practitioner in England and Scotland, particularly as affected by recent legislation with respect to workmen's compensation.

CHANGES IN THE BODILY FATS FROM PUTREFACTION. M. KERNBACH, V. FISI and D. BERARIU, Ann. de méd. lég. **7**:598, 1927.

Postmortem decomposition has been investigated for hygienic, toxicologic and medicolegal purposes, the last especially, mainly to determine the approximate time of death. This study from Kolosvar (Cluj) in Roumania is based on histochemical data supplemented with polariscopic examinations. It was undertaken to ascertain the extent with which a regular sequence of modifications occurs in the fats and lipoids after death and its possible practical applications. After five dogs were asphyxiated and buried, adipose tissue was taken from their bodies at frequent intervals for many months; this tissue was also taken from the bodies of six infants or fetuses and three adults soon after death, from five other adult bodies and one fetus at intervals of from seven to fifty-nine days after death.

It was learned that the more complicated compounds containing fats, the lipoids, do not undergo any regular alteration. The neutral fats, such as react vividly to sudan III, begin to lose their familiar staining properties about fifteen days after death but regain them about six weeks later. It is suggested that this is due to mixing of both saturated and unsaturated acids with the soaps. The soaps and fatty acids begin to appear after two months, and after about another month the soaps disappear. The fatty acids persist for a long time. Interesting variations of structure of the fats, of their staining reactions and of the formation of crystals were observed. The authors believe that these examinations offer a substantial help in estimating the time of death.

E. R. LE COUNT.

CHANGES IN THE HUMAN UTERINE CERVIX DUE TO PREGNANCY. H. STIEVE, Anat. Anz. **36**:51, 1927.

The structure, functions and modifications of the region where the uterine body and the cervix meet during pregnancy were matters of a great deal of study and controversy among obstetricians for many years. This ceased to a large extent with the general acceptance of the views that a third portion, the isthmus, intervenes between the cervix and body and that the wall distal to the isthmus, the cervix proper, has no part in, and remains unchanged by, pregnancy.

The latter conception is vigorously, and apparently successfully, controverted by results of examinations that Stieve made of the cervix of seventeen nulliparous, forty-five parous and five recently delivered uteruses. He found that the structure of the cervix changes during the first month of pregnancy. It becomes larger and much softer. The fibromuscular wall takes on the characteristics of granulation tissue; the glands become wider, grow more deeply into the wall and become filled with mucus.

The epithelium of the glands multiplies, and new glands form. The tissue between the glands is reduced to delicate sheaths. Out in the wall many vessels appear, especially large veins. Up to the third month of pregnancy, the muscle fibers increase in size and number in the cervix. At this time the isthmus opens up, and its wall unites with that of the body to contain the growing gestation sac and fetus. The increase in thickness affects both cervix and isthmus, but the isthmus alone increases in length.

The cervix proper gradually assumes the structure of erectile tissue, and distention of the veins has an important part here in closing the canal, as is the case with the anus and proximal end of the urethra. At the end of pregnancy and as a consequence of such alterations, the cervix is a highly vascular knob, its inner part consisting almost entirely of mucus. When birth occurs, the mucus and glands are swept away, and only a little epithelium remains deep in the cervix wall from which new glands form. Just after birth the cervix is longer, wider and has a thinner wall; the vaginal process is much larger, and the glands in its lining are small and are limited in number. The blood vessels in the cervix fill up again at once after birth. The cervix swells up like a sausage, and the cavity of the uterus is closed off again from the vagina. During the puerperium, the glands of the cervix are replaced sooner than those in the isthmus. The

collagen fibers in the wall which previously loosened and separated to allow the cervix to dilate during labor and not to tear, return to their former compact arrangement.

E. R. Le Count.

Postmortem Rigor of the Heart. H. Meltzer, Arch. f. d. ges. Physiol. **218**:115, 1927.

Rigor of the heart of dogs, cats, rabbits, sheep, goats and guinea-pigs was measured with Mangold's sclerometer, followed throughout its course in a moist chamber at a temperature of from 17 to 20 C. and found first in the interventricular septum. It appeared in the left ventricle before it did in the right where the maximum firmness is first attained. Rigor began just beneath the endocardium. In the heart of dogs, it lasted seventy-two hours. Contraction may be provoked by mechanical irritation after the muscle is firm with rigor. This was explained by scattered unchanged muscle cells.

E. R. Le Count.

Embolism of Fat. H. G. Zwerg, Beitr. z. klin. Chir. **141**:268, 1927.

In the marrow of long bones of children the fat contains more palmitin than it does during later years, and less fat is present than is found in the long bones of adults. Embolism of fat is most serious during the third to the fifth decades of life. It rarely causes death. In one clinic in which during three years 929 patients were treated for fractured bones, only three died of embolism of fat, and in a second clinic only three deaths occurred during ten years. Crushing injuries of several bones are responsible for severe embolism of fat.

Considerable difficulty has been encountered in applying all the results of experimental embolism of fat in animals to the problems of embolism of fat in man; this apparently is due to slight differences in anatomic structure, the chemical composition of fats and the nature of the injuries. Zwerg made injections of dog fat into dogs. In some experiments the fat contained iodine and was therefore demonstrable with fluoroscopy; in others sudan III was used, so that the fat could be seen as it coursed through glass cannulas inserted in blood vessels.

Zwerg concluded that the outcome of embolism of fat depended a great deal on the state of the heart; that only a little got through the pulmonary capillaries into the systemic arteries, and that little harm then resulted. He found, as others have, that fat lodged in the lungs may remain there a long time. When injections of epinephrine were made, the amount necessary to kill the dogs was increased one half. When the amount piled up in the pulmonary capillaries is gradually increased, the chambers of the right side of the heart may dilate, and that which filters through the lungs may cause fatal embolism of the brain.

The author emphasizes careful handling of the bones when they are operated on; they should not sustain any concussion and as little hemorrhage as possible should occur so that the fat in the marrow is not compressed. The capillaries of the lungs are easily distended and with a healthy, vigorous heart, enough blood is pushed through vessels unobstructed by fat. Injuries of bones accompanied by shock and the weakened heart action with which shock is associated may cause fatal embolism. A careful examination of the heart is especially indicated before operation on bones should be undertaken.

E. R. Le Count.

Bullet Wounds of the Atlas. I. G. Knoflach, Deutsche Ztschr. f. Chir. **202**:366, 1927.

Reports of bullet wounds of the spine come mainly from surgeons and from surgical clinics. Because death frequently occurs at once or before there is any surgical treatment when the cervical vertebrae are injured, fewer reports of injuries of this part of the spine from bullets and other missiles are found. In the summary of this article, only one third of 300 bullet wounds of the vertebrae were penetrating, and only ten were wounds of the cervical vertebrae. Two wounds caused by shrapnel and fractures of the atlas are reported; both of the patients recovered,

one with and one without operation. A third type of wound was the more common injury of the atlas from a shot in the mouth, in an attempt at suicide. This patient also recovered without operation. The report deals mainly with roentgen diagnosis. The atlas and other vertebrae may be considerably injured in this region without many symptoms referable to damage to the cord, because the spinal canal is relatively roomy at the upper end. One missile lodged so as to project into the joint between the atlas and one of the occipital condyles.

E. R. Le Count.

Esophageal Diverticulum Due to a Fall. Bertrams, Deutsche Ztschr. f. Chir. **205**:134, 1927.

A man fell about 10 feet and landed so that the left side of the neck was severely bruised. He experienced difficulty in swallowing at once and suffered thereafter from a feeling as though the neck was swollen, especially when he ate hurriedly. Another accident occurred thirteen years later while the patient was in the water; when he spit out some of the water, he noticed that it was bloody. Following this, a clucking sound in the throat and some regurgitation of food appeared. He lost 26 pounds (11.8 Kg.) because of the difficulty in eating. At operation a diverticulum of the esophagus was found high up on the left side where congenitally there is less muscle in the wall. This region is known as Laimer's triangle and is at the level of the cricoid cartilage of the larynx. In microscopic preparations of the wall of the pouch, muscle fibers, abundant at the base, gradually thinned out toward the apex where there were none. Most of the symptoms that occurred during the thirteen years between the two accidents were attributed to spasm rather than to the actual pulsion diverticulum found after the second accident. The first accident simply separated the muscle fibers somewhat.

E. R. Le Count.

Injury Contributing to Death from Ruptured Aortic Aneurysm. C. Klieneberger, Med. Klin. **23**:1069, 1927.

Indemnification was secured for a person who sustained accidental injuries by falling about 5½ feet and being crushed by bales of cotton waste which rolled from a truck. Three right ribs were broken, and because subcutaneous emphysema of the chest developed at once, the condition was diagnosed as torn lung tissue.

After the accident a cough with bloody sputum developed; it grew worse with heavy work. Although death did not occur until two years after the injury, it was decided that this interval did not constitute a competent objection to the causal relation of the injury to the rupture of an aortic aneurysm into the trachea. Unfortunately, postmortem examination was not made.

E. R. Le Count.

Crushing Injury of a Cervical Vertebra; Death Two Years Later from Pharyngeal Cancer; no Connection. P. Frank, Med. Klin. **23**:1267, 1927.

It was claimed that the head and neck of a man were injured by the heavy cover of a ventilator when he attempted to remove it. This occurred on Sept. 22, 1922, and he did not resume work until twenty months later. In June, 1924, a huge carcinoma of the pharynx was discovered, and the claim made that it was a sequence of the injury. A professor from the Institute for Cancer Research in Berlin supported this view, and two physicians expressed a similar opinion. Another professor and Dr. Frank opposed that interpretation, and because of such conflicting ideas the matter was referred to the Director of the Pathological Institute of the University of Berlin. He decided that the tumor was a rapidly growing cancer which began not earlier than April, 1924, and that the growth could not have any relation to the accident one and one-half years before.

E. R. Le Count.

ABSCESS OF THE BRAIN AFTER WOUNDS. J. PETŘIVALSKY, Bratisl. lékař. listy. **7**:121 and 226, 1927.

The results obtained at a garrison hospital in Prague in the surgical treatment of abscesses of the brain in twenty-three patients following war wounds are described. With this is a thorough review of sixty-three contributions to the subject, most of them recent. Secondary infection of wounds of the head are fully as dangerous as primary infections, and infection with *B. coli* is especially dangerous because there is little disposition of the suppuration to become localized. Only eight of the twenty-three patients were treated later than three months after injury; in twelve, recovery occurred.

E. R. LE COUNT.

Technical

LESIONS IN THE BRAIN IN DEATH FROM FREEZING. LAURETTA BENDER, Arch. Neurol. & Psychiat. **20**:319, 1928.

In a person frozen to death, congestion and miliary hemorrhages were found in all parts of the brain, nerve cells of which showed severe vacuolization. Similar changes appear to occur in the guinea-pig and rabbit killed by freezing.

THE ISOLATION AND ESTIMATION OF CLOSTRIDIUM WELCHII. GEORGE H. CHAPMAN, J. Bact. **16**:49, 1928.

Clostridium welchii in pure culture can be readily obtained from biologic material which is incubated on blood agar plates at 48 C. in a phosphorus jar. This method avoids the necessity of preliminary heating to destroy vegetative forms and is also specific for *C. welchii* as compared with other anaerobes.

TRAUMATIC RUPTURE OF THE BLADDER AND URETHRA. W. C. STIRLING, J. Urol. **17**:503, 1927.

Of seven cases reported, four were from automobile or motorcycle accidents. With prompt operation, the mortality of nearly 90 per cent is cut in half. When operation is delayed twenty-four hours, the mortality is 75 per cent. In one interesting case, the rupture of the urethra resulted from falling astride the wheel of a buggy sixty-five years before; since that time the patient had catheterized himself with a silver catheter and followed withdrawal of the urine with a douche of boric acid. Where the catheter struck the lining of the wall of the bladder, a carcinoma developed which caused death from metastasis after an operation.

E. R. LE COUNT.

A NEW METHOD OF FIXATION AND STAINING OF TISSUES OF THE CENTRAL NERVOUS SYSTEM FOR STUDY OF THE CYTOARCHITECTURE. G. CARL HUBER, Warthin Ann. Vol. pp. 1-12, 1927.

Huber describes a method of fixation and staining of tissues of the central nervous system which has yielded reliable results. The fixing solution consists of 1.5 Gm. acid trichloracetic (Mallinckrodt) and 3 Gm. mercuric chloride, C.P. (Mallinckrodt), added to 100 cc. ethyl alcohol, 95 per cent. Larger pieces are more rapidly and uniformly fixed by this solution than by older methods. Extremely large pieces require several days for complete fixation, and it is wise to renew the fixing fluid at intervals of two days. After complete fixation, the fixing fluid is decanted and is replaced by 95 per cent ethyl alcohol which is renewed a number of times. It is not necessary to wash out the mercury salt. After thorough dehydration, and clearing in xylol, the tissue is embedded and cut in paraffin.

In cutting serial sections, from 40 to 50 microns in thickness, it has been found advantageous to use a sliding microtome, with an automatic feed detached, together with a strong thick knife placed obliquely to the sliding bed. The "water on the knife" method gives the best results with brain sections. The sections are

transferred to a slide which is coated with albumin fixative, and placed obliquely in a deep Petri dish nearly filled with distilled water. After the requisite number of sections are placed on a slide, they are flattened on a warm oven and then carried through xylol and graded alcohols to distilled water.

The slides are placed upright in oblong staining dishes and covered with a 0.1 per cent aqueous solution of toluidine blue (Grüber) for from fifteen to eighteen hours, which is replaced by several changes of distilled water. The dish then is filled with a solution of lithium carbonate (100 cc. saturated aqueous solution of lithium carbonate and 900 cc. distilled water) for about two hours. Differentiation is then carried out with 70 per cent alcohol until the outline of the nerve cells is evident. The differentiation and the dehydration are completed in 95 per cent and absolute alcohols. The slides are then passed through xylol and are mounted in neutral Canada balsam.

W. M. SIMPSON.

COMPLETE TRANSVERSE RUPTURE OF THE JEJUNUM WITHOUT EXTERNAL WOUND. J. R. ARMSTRONG, Brit. M. J. **1**:1064, 1928.

A man, aged 47, was admitted in shock and with a painful, rigid abdomen. While riding a motorcycle, he had lost control, crashed into a wall and struck his abdomen on a projecting corner. At operation, a complete transverse rupture of the jejunum accompanied by a tear of 1 inch in the mesentery was found, 4 inches from the duodenojejunal flexure. Complete recovery followed an end-to-end anastomosis. Armstrong briefly reviews the statistics on this unusual lesion, appends a short anatomic discussion of the relationships between the loops of bowel and their mesentery and concludes that such injuries as that described occur most often in those loops of bowel which are likely to be forced against the spinal column.

GEORGE RUKSTINAT.

THE DIAGNOSIS OF SYPHILIS BY FLUCTUATION OF SERUM OF THE BLOOD WITH CHOLESTERINIZED EXTRACTS (CITOCHOLREACTION AND LENTOCHOLREACTION). H. SACHS and E. WHITEBSKY, Klin. Wchnschr. **7**:1233, 1928.

The beef heart extract of the Sachs-Georgi reaction (one part moist weight to five parts alcohol) is evaporated, dissolved again in one third the original volume of alcohol and added to from 0.3 to 0.6 per cent of cholesterol. In contrast with the original slow reaction (lentocholreaction) the following rapid procedure is designated the citocholreaction:

The concentrated extract is diluted rapidly with two parts of an 0.85 per cent solution of sodium chloride and allowed to stand for ten minutes at room temperature. Two tenths of a cubic centimeter of serum of the blood, inactivated for thirty minutes at 55 C. is mixed with 0.1 cc. of the diluted extract. The mixture is thoroughly shaken for from five to ten seconds and then left at room temperature for thirty minutes. One cubic centimeter of an 0.85 per cent solution of sodium chloride is added, and the reading is made at once either macroscopically or with an agglutinoscope. As a control, the diluted extract is replaced by a corresponding dilution of alcohol.

The results seem favorable.

E. F. HIRSCH.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

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ESMOND R. LONG, *President, in the Chair*

SOME FACTORS IN NATIVE IMMUNITY TO TUBERCULOSIS. ESMOND R. LONG.

I have chosen for the subject of my paper one that has been a favorite on occasions of this sort, a phase of the broad subject of natural immunity. I am inclined to believe that this subject finds its way into such addresses so frequently because its mechanism is still almost entirely in the realm of speculation, and it is only in the safety zone of a presidential address that the surmises and hypotheses conventionally applied can escape immediate critical assault.

It seems to me that the importance of native immunity to tuberculosis is again engaging the attention of pathologists, which for some time past has been largely directed toward the more spectacular phenomena of acquired resistance to this disease. Twenty years ago, when the newly discovered skin reactions emphasized anew the enormous extent of tuberculous infection in the human race, and at the same time disclosed the surprising youth at which this infection occurs, the fact of an apparent universal susceptibility to infection with still an obvious resistance to further inroads of the disease soon led to a widely prevalent recognition of these first infections as immunizing or spontaneously "vaccinating" inoculations.

The experimental investigations of Paul Römer on the protective effect of nonlethal inoculations of tubercle bacilli against later heavier infection supplemented and extended the classic observations of Robert Koch on the phenomenon linked with his name. Twenty years of effort to make practical prophylactic use of the knowledge thus gained are culminating at present in the gigantic experiment on man of Calmette, and for these two decades there has been unceasing experimental inquiry into the underlying mechanism of the protection thus conferred.

Not from any lack of success attending these efforts, but apparently in response to a natural law of human behavior compelling a constant review of the steps, the pendulum of inquiry is again swinging back to a consideration of factors temporarily lost from sight while the phenomena of hypersensitiveness and acquired immunity held the chief attention. Certain unanswered questions are again in the fore. There is not time at present to discuss many of these, but attention may be directed with profit to one, the arrest of the initial infection. I am sure that this is a puzzle as much to the matured phthisiologist, as to the tyro medical student, who naively gives the information that infection in children meets with little resistance to its rapid and ultimately lethal progression, and almost in the same breath parrots the astonishing paradox that 50 per cent or more of children are infected before they reach the age of 6.

The wide variability in the anatomic extent of these first infections, ranging from a small fibroid scar to a large calcified primary complex, must have impressed everyone with moderate experience in the postmortem room. Beyond question some of this variation is to be attributed to difference in dosage and virulence of the infecting bacilli, but the undoubted cases in which known massive and repeated exposure has not led to even initially extensive infection, testify sufficiently that the bacillary factor is not the only one involved. Such cases rule out as well a dominant rôle of locational accident in determining the outcome of early infections.

This raises at once the old question of a varying inherent immunity to tuberculosis in the human race. And it is at this point that one must begin distinguishing immunity and resistance. In true conformity with a militaristic upbringing we have built our young and vigorous science of immunology into a picturesque belligerency, in which leukocytes attack germs, serum antibodies fight their progress and connective tissue cells hem them in like an investing and relentless wall of besiegers — a vivid antimicrobial warfare with all the traditional interaction of armed conflict.

In the face of this deeply noted tradition the other possibility, a simple insusceptibility, is not particularly alluring. To change the analogy into a more pacific cast, we have remembered the encompassing thorns but have largely forgotten the stony places which equally made fruitless the freshly sown seed in the parable. And yet, as I hope to be able to show later, if we utterly neglect the latter point of view, we are perhaps missing half of our opportunity to understand immunity to initial infection.

The conventional view of resistance to tuberculosis is the one which emphasizes the obviously protective aspect of its anatomic unit, the tubercle. The epithelial-like cells, with their attribute of phagocytosis, meet every advance of the spreading germs with an encircling investment. It would seem as if this mechanical limitation, supplemented by a destructive phagocytic activity of the cells, might well arrest the process. That it frequently does not do so has been usually explained on the ground that the destructive or lytic activity of the phagocytic cell may not always be effective, and that so far from killing off the germs the motile phagocytic cells may actually transport them alive to set up infection in a new place.

In recent years, almost in recent months, a startling reversal of the original Metchnikovian view of phagocytosis has been put forth. White, Sabin, Doan, Cunningham and others are submitting increasing evidence suggesting that so far from being a means of defense the tubercle may in effect constitute a protective mechanism for the germ through its provision of a favorable environment for the growth of the latter in the epithelioid cell. One of them has even hazarded the opinion that were it not for epithelioid cells of a certain type, tubercle bacilli introduced into the body would fail to find the proper medium for their multiplication, and would shortly die out. This is a far cry from the original view of the epithelioid cell as a defensive agent.

A proper appreciation of the evidence on which this new theory is based requires much understanding of the intricate problem of the origin and ultimate fate of the epithelioid cells. Unfortunately, there is no general agreement on this subject. The hypothesis to which I have just made reference rests on the identification of two types of epithelioid cells, the monocyte, a blood cell derived from extravascular cells in the reticulated organs of the body, such as the spleen, bone marrow and lungs, and the clasmatocyte, a cell of the fixed tissues derived originally from embryonic endothelium. Sabin, Doan and Cunningham presented evidence that the predominant epithelioid cell in progressive tuberculosis is the monocyte. Moreover, they appear to have established the important fact that the monocyte count of the circulating blood furnishes a reliable index of the type of tuberculosis in the tissues, progressive or otherwise. Their counts show a significant ratio between the monocytes and the circulating lymphocytes, with the former relatively high in cases with poor prognosis and relatively low in favorable cases. The results of Morriss and Tan, at Gaylord Farm, and of my associates Dr. Seibert and Dr. Finner, seem to support this belief.

In sharp and apparently irreconcilable contrast with the views of the Sabin group stands the work of the veteran cytologist Maximow, who also discovered both monocytes and clasmatocytes in the epithelioid tubercle, but failed to find the variations in their significance stressed by Sabin and her colleagues. In investigation on tissue culture Maximow seems to have established an intimate genetic relation between the lymphocytes and the other important cells of the

tubercle, viz., the epithelioid cell and the fibroblast. "The source of the epithelioid cells," Maximow stated, "is double; some are mobilized histiocytes" (i. e., clasmatocytes in another terminology) "and some are hypertrophied lymphocytes." "Under appropriate conditions of time and stimulus," he added, "the epithelioid cells in turn become fibroblasts."

Thus, Sabin, Doan and Cunningham stressed the significance of varying proportions of lymphocytes and monocytes, while Maximow found them essentially one and the same cell. Pathohistologists are particularly receptive to the Maximow view because its emphasis on the relation of lymphocytes to both the epithelioid cells and the fibroblasts goes far to explain that outlying ring of lymphocytes which has so long puzzled the student of the tubercle.

Whether improvement of the already masterly technic of these able and tireless investigators will bring them together remains to be seen. If it does not it will not be for want of industry. In the meantime those of us who are not skilled cytologists, but are interested in the same general problem, can undertake experiments only of a less ambitious character. I have wondered if a comparison of the immediate cellular response, as shown in ordinary fixed tissues, to the implantation of tubercle bacilli in animals of known widely varying resistance to the disease, might not shed light on the problem of native immunity. I was led to undertake this partly through a greater familiarity with the cellular reaction of acquired immunity. It is an old view, which has recently been concisely stated by Theobald Smith, that "acquired resistance is only a specific increment of natural resistance, either through a temporary mobilization of natural forces, or the more prolonged overactivity of some element of natural resistance." To test this view in its cellular aspects, my assistant, Mr. Vorwald, and I, in experiments to be reported by him in detail later, have studied one day, one week and one month tubercles in the guinea-pig, monkey, rabbit, rat, dog, cat, chicken and turtle following inoculation with a standard dose of human type tubercle bacilli per kilogram of weight.

While the results of this experiment are highly complicated and cannot at the same time be briefly and adequately summarized, they show clearly that the speed of initial reaction cannot be correlated with an ultimately favorable outcome. The most susceptible animal, the guinea-pig, showed the most prompt and extensive reaction to the implantation of tubercle bacilli in the lung. In contrast, the far more resistant rat scarcely reacted within twenty-four hours, but in the succeeding weeks constructed small, tight, epithelioid tubercles, with a notable economy of cells compared with the lavish outpouring in the susceptible guinea-pig. The monkey, ultimately almost as little resistant as the guinea-pig, exhibited far less reaction at the start, but massive tubercles at the end of a month. The tubercles of the rabbit resembled those of the rat cytologically, but were larger and more progressive, without approaching those of the guinea-pig or monkey in extent.

In brief, these simple experiments have seemed to me to support a view that I have held for some time that we must look beyond the solid, formed elements of the body for some part of the story of native insusceptibility to tuberculosis, and consider the capacity of the bacillus to take hold on the soil in which implanted, or, less metaphorically, to multiply on the unorganized chemical nutriment provided. Fortunately, we are well provided with information on the nutritional requirements of the tubercle bacillus. As a matter of fact one nutritional requirement is outstanding, as far as can be determined by in vitro experiment. Of all carbon compounds the triatomic alcohol glycerol best supports the growth of the micro-organism. It is the basic substance for the synthesis of the characteristic lipoids of the bacillus and can support active growth as the sole source of carbon.

It seems to me that the time has arrived for an attempt at closer correlation of the knowledge of the nutritional factors of the bacillus and its growth in the human body. Unfortunately, the technical difficulties are as great in their own way as in the morphologic experiments to which I have referred. Our attempts to determine whether differences exist in nutritional availability for the tubercle

bacillus in tissues of varying resistance have so far proved futile. On the other hand, indirect evidence from experiment has been highly suggestive. I wish, however, to lay little stress on the present results of these experiments, as first experiments have a notorious tendency to be strongly and honestly positive, while incapable of repetition. I may mention them, however, for what they are worth in their bearing on our problem. On the theory that glycerol might be a controlling chemical factor in the growth of the bacillus within the body as well as outside, an attempt was made to decrease the resistance of a relatively refractory animal by increasing its glycerol content, and to enhance that of a susceptible animal by decreasing any naturally existing glycerol in its tissues. For the first purpose, glycerol was injected intravenously into infected rats several times a day for a period of two months; similarly infected but nontreated rats served as controls. For the second purpose, palmitic acid was fed in large quantities to infected guinea-pigs, on the theory that in conformance with the law of mass action an excess of a fatty acid would force the synthesis of any glycerol freed from fat in its metabolism back into the form of neutral fat.

The results were clearcut as far as they went. The rats treated with glycerol developed a more rapid and extensive pulmonary tuberculosis than did the nontreated rats used as controls. The guinea-pigs treated with palmitic acid developed less pulmonary tuberculosis and a more sclerotic type than the nontreated rats used as controls.

For the reasons given, I think that these experiments are deserving only of mention and not of stress at the present time, but I would call attention to certain clinical facts which seem to me to be worthy of more detailed notice than they ordinarily receive. These have to do with a number of traditional incompatibilities as well as susceptibilities in respect to tuberculosis and other diseases. In a recent admirable review on the pathogenesis of tuberculosis, Allen Krause pointed out again that we have not yet learned why in diabetes and obesity — to mention in particular two of the abnormal constitutional states associated with a modified resistance to tuberculosis — resistance is so altered. I may quote his statements, which cannot be improved, "In our ignorance it is significant that diabetes, a so-called disease of metabolism, is associated with an unusual tendency to active tuberculosis." And again, "What now becomes of interest is the undeniable fact that obesity provides peculiarly sterile soil for tuberculous infection. How it does this is peculiarly inexplicable."

I believe it would not be overrash at this time to suggest an explanation for these interesting facts. As I stated at the outset it is perhaps a privilege in such an address as this to offer hypotheses without the usual insistence on rigid proof. Both of the pathologic states I mentioned are diseases of fat metabolism. In the one, diabetes, associated with susceptibility to tuberculosis, the trend of fat metabolism is catalytic, by way of substitution for an impeded sugar metabolism. With the break-up of every molecule of fat, glycerol is presumably liberated. While the amount in circulation at any one time is probably small, the constant increased availability of the substance, even if slight, ultimately might be of great significance for the growth of the tubercle bacillus.

On the other hand, in constitutional obesity, the trend of fat metabolism is predominately synthetic. For a reason not yet known, but related in some way to the influences controlling reversible reactions, fat tends to be stored up as neutral fat. This probably means that less of the labile intermediaries of fat metabolism, including glycerol, are in circulation. It would not be surprising if in the face of this constitutional impoverishment in the substance best supporting its growth the tubercle bacillus failed to thrive.

I would not for one moment suggest that these chemical factors are the determining ones in native immunity to tuberculosis. I proposed at the outset to discuss only some of the factors bearing on this subject. I simply wish to point out that they should not be overlooked, and that in a disease in which a slight influence could tip the scales of cellular activity in either direction, these constitu-

tional chemical factors of the soil could be important. I would be bold enough to wish to modify, as committing its author too far, even that conservative explanation of natural immunity to tuberculosis offered by Theobald Smith in his presidential address before the National Tuberculosis Association. His cautious statement that "the primary resistance of the host is due to forces inherent in the system," if by resistance be implied immunity, leaves out the fact that to some extent the system may be passive and nonreactive and yet be respectively more or less insusceptible. When the truth is finally known, I am sure it will develop that native immunity to tuberculosis is the resultant of the interplay of many factors so intimately connected that distinctions on specific morphologic or chemical bases will be impossible.

TORULAR LEPTOMENINGITIS. C. B. SEMERAK.

Lesions caused by *Torula histolytica* are chiefly in the meninges, although the involvement of other tissues, such as the lungs, has been observed. The symptoms of torula infection of the meninges are those of meningeal irritation or tumor of the brain. The organisms are demonstrated by careful examination of stained preparations of the spinal fluid and by cultures. The onset is insidious, and the illness is protracted. The lesions, usually limited to the pia-arachnoid, are like cysts filled with organisms in a colloid substance. The inflammatory reaction is slight. My report is the study of two brains from patients with torular meningitis.

CASE 1.—The clinical and anatomic observations are published in the *Archives of Neurology and Psychiatry* (**19**:689 [April] 1928). The dura mater was unchanged except for a region 4 by 3 cm. on the visceral surface, which was dark brown with many small hemorrhages. This discoloration was opposite a surgical laceration and hemorrhage in the right frontal and temporal regions of the brain, 4 by 3 cm., elevated 1.5 cm. A gauze-wick drain, 7 cm. long and 2 cm. wide, protruded from the lower margin. The right cerebral hemisphere was swollen, the convolutions flattened and the sulci narrow. The flattening of the convolutions of the left hemisphere was much less. The leptomeninges, lifted away from the cortex by an opaque fluid, were thin and transparent except for a few irregular hemorrhages on the right side, continuous or near the traumatized cortex. There were no hemorrhages on the left side, with only a slight staining with blood along the distended veins. The arteries at the base of the brain were unchanged. There was a pressure groove (foramen magnum) on the inferior surface of the cerebellum. The surfaces made when the cerebrum was cut were normally stippled, and the ventricles were slightly distended, 11 mm. transversely, at the level of the anterior commissure. The ventricular ependyma was blood-stained and finely granular; the choroid plexus was unchanged. The decompression hemorrhage and traumatized tissues included the island of Reil, extended from the inferior frontal gyrus to the inferior temporal gyrus, and were bounded medially by the external capsule and central nuclei. In this region the cortex and the corona radiata were destroyed. There were no gross changes in the brain stem or cerebellum. The spinal dura was grossly normal. The leptomeninges were thin and transparent, but were slightly raised by a gelatinous substance (coagulated protein). On sectioning the surfaces were found to be white.

Sections were examined from the left inferior frontal and superior temporal gyrus, the right inferior and medial frontal gyrus, the left superior and medial frontal gyrus, the right postcentral gyrus, the cornu ammonis, the brain stem at the aqueduct of Sylvius, the right crus cerebri, the left lenticular nucleus, the thalamus with the substantia nigra and the nucleus ruber, the pons, the left dentate nucleus with the surrounding arborizations, the medulla and the cervical, thoracic, lumbar and sacral portions of the spinal cord. The tissues were stained with hematoxylin-eosin, hematoxylin with phosphotungstic acid, Mann and van Gieson stains, Nissl's toluidine blue, sudan III and the Rio del Hortega stain. The

connective tissue bands of the cerebral leptomeninges were heavy; their meshes were widely distended, and between them were masses of torula organisms. These varied greatly in size, the smallest, about 8 microns in diameter, were stained darkly and could easily be mistaken for lymphocytes, the largest as much as 50 microns in diameter had a homogeneous body with a darkly stained capsule, from 1 to 2 microns thick. Some of these were budding. There was a dense lymphocytic infiltration about the arteries and veins with an occasional plasma cell and a few large multinucleated phagocytes containing one or several torula organisms. About the vessels of the bulbar and spinal pia-arachnoid there was a lymphocytic exudate, and torula cells were scattered between the meshes to a lesser extent than in the cerebral leptomeninges. There was also a perivascular lymphocytic infiltration in the gray and white matter of the cerebrum, brain stem, pons, medulla, spinal cord and cerebellum. Many yeast cells were scattered in the perivascular lymph spaces, with only a few in the nervous tissue. At the outer margin of the left dentate nucleus was a necrotic region, 7 by 3 mm. in diameter, and a few torula organisms were in the cellular debris. The ganglion cells of the dentate nucleus were swollen, faintly stained or contracted and narrow, and the chromatin was stained intensely. A few cells situated at the periphery of the necrotic region were simply shadows, without nuclei or Nissl granules. Between the necrotic region and the cerebellar arborization of the cortex was a slit about 6 mm. long and 1 mm. wide, with ependymal cells along its periphery, representing the terminal portion of the lateral recess. In this there were a few large giant cells with one or several torula organisms, also many extracellular organisms. Some of the smaller arteries were thick-walled. Most of the veins were empty, occasionally, however, a distended vein completely filled the perivascular lymph space. There were changes in the large ganglion cells, except that the Nissl granules were more or less absent. There was no increase in glia cells or glia fibrils.

The histologic diagnosis was: torular cerebrospinal leptomeningitis; multiple petechial hemorrhages of the leptomeninges; marked perivascular lymphocytic infiltration of the brain, medulla and spinal cord; edema of the brain and leptomeninges; anemia of the brain; slight internal hydrocephalus; slight focal necrosis of the cerebellum; large surgical laceration of the right temporal lobe, and postoperative pressure asymmetry of the brain.

Case 2.—The essential clinical features of the condition in this patient, a negress, aged 39 years, will be published elsewhere. These features are comparable to those of the first patient. (The postmortem examination was made by Edwin F. Hirsch.) The reflected tissues of the scalp were unchanged, the calvarium was 1.5 cm. thick, the dura was tense and the dural sinuses were unchanged. Between the dura and the pia-arachnoid were delicate weblike adhesions. The convolutions of the cerebrum, especially of the right hemisphere, were flattened. On both sides of the longitudinal fissure over the vertex was a milky opacity 4.5 by 1.5 cm. In the leptomeninges covering the sulci and on the base of the brain were other opacities, from 1 to 2 mm. in diameter. About the optic chiasma was a thin fibrous tissue thickening. Considerable quantities of faintly turbid spinal fluid escaped from these tissues. The brain with the upper half of the dura weighed 1,330 Gm. The anterior poles of the temporal lobes were adherent to the inside of the dura, and when the brain was removed these portions were torn. There was a melanin pigmentation of the base of the brain and upper part of the spinal cord. After the brain was removed, the dura of the front of the middle cranial fossa was covered on both sides, in a place 2 by 2 cm., with soft red-brown tissue partly brain substance and partly granulation tissue. On the opposite surfaces of the dura in these places there were masses of white granular tissue, singly and confluent, from 1 to 2 mm. in diameter, that were distributed along the course of the middle meningeal arteries. They lay in corresponding excavated places of the bone. Those on the right side were especially numerous about the gasserian ganglion, on the left side less so about the gasserian

ganglion, although the erosions of the bone were otherwise more extensive. There were no changes in the middle ears, ethmoid and sphenoid sinuses. The left maxillary sinus contained some soft, red tissue; the right was unchanged.

The brain was symmetrical, the cerebral convolutions flat and the sulci shallow, especially on the right side. The leptomeninges, lifted from the cortex by a turbid fluid, were thin and moderately transparent except for a milky opacity over the vertex, along the longitudinal fissure for about from 1.5 to 2 cm. on each side. There were multiple white fibrous thickenings scattered in the sulci along the veins in the pia-arachnoid, from 0.5 to 1.5 mm. in diameter, and also in the interpeduncular space, and an opacity at the tip of the left frontal lobe and along the left Sylvian fissure. On both sides of the fissure of Rolando, at about 3 cm. from the longitudinal fissure, there was a dark brown discoloration of the leptomeninges, about 1 cm. in diameter, and another in the center of the left frontal lobe, about 7 by 12 mm. in diameter. The veins of the leptomeninges were considerably engorged and their finer radicals formed a dense network all over the cerebral hemispheres. The arteries at the base of the brain were slightly thickened and gaping, and the basilar artery was markedly tortuous. There was a deep, well circumscribed (foramen magnum) pressure furrow of the cerebellum, and the leptomeninges at the base, especially toward the midline, were opaque. The surfaces made by cutting were stippled; all the ventricles were greatly distended; the lateral ventricles were 2.5 cm. transversely at the level of the anterior commissure; the anterior and posterior horns were wide and deep, especially the right; the ventricular ependyma and the septum pellucidum were soft and swollen; the choroid plexus was grossly unchanged, and the gray and white matter were well differentiated. The internal surface of the spinal dura was glistening and smooth, the spinal pia-arachnoid was thick and transparent and its veins were dilated. There was a dark brown blood stain in the lumbar region. There were no other gross changes in the brain and spinal cord.

The following sections were examined microscopically: left inferior frontal cortex with corona radiata and pia-arachnoid, right corpus striatum with internal capsule, thalamus, substantia nigra, right cornu ammonis, medulla, pons, dentate nucleus and the spinal cord at the regio cervicalis, thoracalis, lumbalis and sacralis. The pia-arachnoid was thickened over the motor cortex, the fibrils were loose, swollen and pushed apart, and in their meshes were disseminated lymphocytes and mononuclear leukocytes in about equal proportion; a few epithelioid and plasma cells and brown, melanin deposits were also present. The infiltration was most pronounced about the vessels and mostly in and about the arterial adventitia. Six spherical, ill defined cells resembling torula were found, but the capsules were indistinct and only examination by oil immersion made possible their differentiation from the surrounding cellular exudate. On the outer surface of the arachnoid over the motor cortex there was a fibrous thickening about 2 mm. long, which consisted of from five to seven rows of fibroblasts, lymphocytes and one large torula cell. In the cornu ammonis there was a massive infiltration of lymphocytes about the ependymal vessels, completely filling the perivascular lymph spaces which were distended and in some instances extended into the surrounding tissue; a few plasma cells and two torula cells were found. The ependymal lining was partly disrupted and partly thickened by from three to four rows of cells, and in one region there was a huge giant cell enclosing a mass of minute torula cells. The basal leptomeninges were also densely infiltrated, especially about the vessels and nerve sheaths, and the perivascular lymphocytic infiltration extended to some vessels at the basal margin of the pons. In the pia-arachnoid of the medulla there were similar changes, that is, a perivascular lymphocytic infiltration which extended to the ependymal vessels where it was most pronounced. All along the ependymal lining of the fourth ventricle there was a cellular exudate consisting of lymphocytes, mononuclear leukocytes and plasma cells. The spinal cord had a marked lymphocytic infiltration at all levels. The pia-arachnoid contained dense masses of lymphocytes throughout, which also involved the sheaths of the peripheral nerves,

which were surrounded by many rows of lymphocytes, penetrating along the sheaths into the nerve bundles. An extensive endarteritis was present in the spinal arteries and in some arterioles of the peripheral nerve bundles. There were dark, melanin masses disseminated throughout the meshes of the spinal leptomeninges. Although the pathologic changes in the spinal cord, especially the lymphocytic infiltration, were marked, there were only a few torula organisms, from two to four in each section, except in the lower lumbar portion about an artery at the incissura anterior where there was a cluster of from fifteen to twenty. The spinal canal was divided in two canaliculi, and there was considerable desquamation of the ependymal cells. The leptomeninges of the cerebellum were also involved in the lymphocytic infiltration but to a moderate extent only; a moderate perivascular infiltration of lymphocytes was also present in both the gray and the white matter throughout the cerebral hemispheres, brain stem, cerebellum, medulla and spinal cord; the subependymal vessels were densely infiltrated in all sections, and there was more or less of a cellular exudate along the ependymal lining. Either the ganglion cells were shrunken or the cell body was swollen and faintly staining, with a pale nucleus and thickened pale-staining neuraxon. There was neither degeneration nor necrosis in any part of the brain, cerebellum or spinal cord.

The histologic diagnosis was: marked subacute torular cerebrospinal leptomeningitis; generalized ependymitis, endarteritis and periarteritis; melanotic pigmentation in the leptomeninges of the brain and spinal cord; marked hyperemia of the brain and leptomeninges; edema of the brain; internal hydrocephalus; hydrops, and atrophy of the large ganglion cells.

Torular meningitis seems to be rare. Accounts of only sixteen of these infections have been published here and abroad during the past twenty-three years. It seems probable that the disease has not been recognized in some patients. The importance, therefore, of repeated spinal punctures in all patients with cerebral or meningeal symptoms cannot be emphasized too much, and the most careful examination of the cells found in the spinal fluid is necessary to differentiate the torula organisms from lymphocytes. That within one year torula meningitis has been recognized in two patients at one hospital suggests that the disease may be more frequent than the relatively few reports on this subject to date indicate.

DISCUSSION

DR. FRANK SMITHIES: Castellani believes that these infections follow the ingestion of the organism and that they are then carried by the blood to the brain.

DR. E. PRIBRAM: Castellani places *Torula histolytica* among the *Cryptococci*. It may be that some infections reach the meninges through the alimentary tract, but I think there are lesions of the mouth, nose or lips and that from these the organisms reach the brain.

DR. E. F. HIRSCH: In both of the postmortem examinations the oldest lesions were about the gasserian ganglions.

THE EXCRETION OF METHYLENE BLUE BY THE BILIARY SYSTEM OF THE RABBIT AND ITS SIGNIFICANCE FOR THE CONCEPTION OF HEPATOGENOUS STASIS IN THE GALLBLADDER. BÉLA HALPERT and MILTON THEODORE HANKE.

Methylene blue (methylthionine chloride, U. S. P.) injected intravenously (2 cc. of a 1 per cent solution per kilogram of body weight) appeared in the bile collected from the ductus choledochus within a few minutes. A sharp rise to the peak of a highest concentration (1:1,100 to 1:3,300), reached approximately within one hour, was followed by a gradual decline to from a fifth to a fifteenth of the highest concentration (1:9,000 and 1:36,000) by the end of the sixth hour. The bile removed from the gallbladder at the same time, i. e., six hours after the injection, usually contained from two to twenty-two times as much of the dye as the last sample of bile collected from the ductus choledochus. At times the concentration of methylene blue in the bile removed from the gallbladder was much higher

(1:720, 1:800) than the highest concentration ever reached in the bile coming from the liver (1:1,100—1:3,300).

Bile collected from the cannulated ductus choledochus between the twelfth and the seventy-second hour after feeding the same amount of dye as used in the injection experiments contained little if any methylene blue. The bile removed from the gallbladder contained the dye in most instances even after seventy-two hours.

The results permit the following conclusions:

The experimental evidence that the bile, at least in the rabbit, does not leave the gallbladder through the cystic duct under ordinary conditions.

They furnish a striking example of stasis in the gallbladder for which the liver is responsible (hepatogenous stasis), i. e., with the bile from the liver a substance, methylene blue, is poured into the gallbladder, the mucosa of which apparently cannot resorb the dye fast enough to cause its rapid disappearance and so the dye remains for days.

They support the idea that something analogous happens in cases of marked cholesterolemia, when the cholesterol content of the bile is correspondingly exaggerated, and thus they throw some light on the formation of biliary concretions.

In view of the possibility of creating conditions analogous to those described here for methylene blue, but with agents with more pronounced bactericidal action, they may indicate the road leading to a much desired goal, a successful chemotherapy of the gallbladder.

TWO HEARTS WITH CHIARI'S NETWORK. WILLIAM HUEPER and ROBERT S. BERGHOFF.

In 1897, Chiari reported (Zieglers Beitr. **22**:1, 1897) an anomaly of the heart, consisting essentially of a netting in the right auricle, which he described as a delicate fenestrum extending from the eustachian valve across the cavum of the right atrium. Since that time, eleven others have been described.

Lesieur and Froment (Lyon méd. **96**:1045, 1911) described a heart with a gaping foramen ovale, and an anomalous thebesian valve, 6 cm. high, stretched across the right atrium. They attributed this to an anomaly of the left venous valve, which failed to fuse with the septum secundum in order to close the foramen ovale. Ebbinghaus (Abbott, M. E., quoted in Osler: Modern Medicine, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 671) described a fenestrated network extending from the eustachian valve across the right atrium, and associated with fifteen small and two large perforations of the interatrial septum. Two other similar anomalies were described by Jordan (ARCH. PATH. **2**:840 [Dec.] 1926) making with our two a total of seventeen cases reported. These two were sent to us from Vienna and are from the laboratory of Prof. Theodore Bauer.

Chiari came to the conclusion that the network is an anomaly, and that the threads are residues of the valvula venosa dextra, and of the septum spurium. In the embryonic development of the heart, the single atrial cavity is divided into two chambers, as is shown in the following. The septum primum arises from the middorsal wall of the atrium and eventually fuses with the endocardial cushions at the junctions of the atrial and ventricular cavities. Perforation of the septum forms the foramen ovale. This is subsequently closed by the fusion of the left valve of the sinous venosus and the septum secundum, which arises in close proximity to the septum primum as an outgrowth from the ventral and caudal wall of the right atrium. The two hearts here presented would have more practical interest if the clinical records were available. Possibly the anomalies caused symptoms.

The heart in figure 1 was 16 cm. in length, 12 cm. in width, with a thickness of the left ventricular wall of 2 cm. There were several fibrous thickenings of the aortic valves. The aorta was dilated and scarred. A delicate network extended

Fig. 1.—Heart, measuring 16 cm. in length, 12 cm. in width, with a thickness of the left ventricular wall of 2 cm.

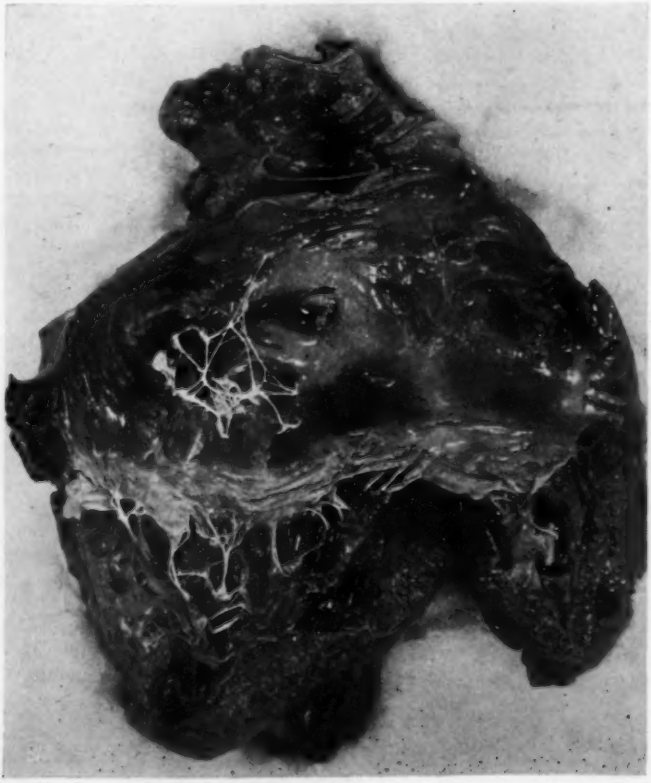

Fig. 2.—Heart, measuring 12 cm. in length, 10 cm. in width, with a thickness of the left ventricular wall of 1.5 cm.

across the cavum from below the eustachian valve, across the thebesian valve. It was fastened by several delicate threads to the septum and the tricuspid valves.

The heart in figure 2 was 12 cm. in length, 10 cm. in width, with a thickness of the left ventricular wall of 1.5 cm. A delicate fenestrated membrane extended across the os of the inferior vena cava, spreading from the upper edge of the os of the inferior vena cava to the eustachian valve and the thebesian valve.

DISCUSSION

DR. R. H. JAFFE: These anomalies are not rare. Rokitanski published illustrations before Chiari wrote his report. There are no associated heart symptoms.

DR. WILLIAM C. HUEPER: Rokitanski illustrated these anomalies, but Chiari described them and explained their anomalous formation.

Book Reviews

THE CORONER AND THE MEDICAL EXAMINER. Issued Under the Auspices of the Committee on Medicolegal Problems. By OSCAR T. SCHULTZ, Director of the Nelson Morris Institute, and E. M. MORGAN, Professor of Law, Law School of Harvard University. With a supplement on Medical Testimony by E. M. Morgan. Bulletin of the National Research Council, July, 1928. Number 64. Paper. Price, $1.50. Pp. 101. Washington, D. C.: National Research Council of the National Academy of Sciences, 1928.

This bulletin is a survey and comparison of the two systems employing, respectively, coroner and medical examiner. It is the first important investigation of the office of coroner in a number of important and typical American cities. Data were obtained by direct investigation and observation and are unquestionably accurate. If this bulletin went no further, it would be of great value. In addition to the large labor of correlating the observations of individual investigators, however, Dr. Schultz and Professor Morgan have given a broad and comprehensive analysis of these observations and offer a genuinely constructive program on this basis.

The coroner system in New Orleans, San Francisco and Chicago, and that of medical examiner in Boston and New York City were investigated. The investigators, who were physicians and lawyers remarkable for ability, integrity and freedom from bias, made the following observations:

The coroner system is so antiquated that it cannot function properly in a modern society.

The position of coroner is an elective one, allowing the choice of a man by local politics regardless of qualifications. Furthermore, the next election may unceremoniously dismiss him despite any excellent work he may have done. This system exposes the coroner to the temptations of present day politics. Whether or not he succumbs to them, he is placed in a position that is unfavorable to the best kind of work. It can be seen that the problem of electing or of appointing coroners is the same as that concerning judges.

In general, the report shows that the system is inefficient, that it is subject to corruption and that it can fail to recognize and cooperate with judicial authority.

The duties of the coroner's office are so manifold and so specialized that one person cannot be expected to have sufficient knowledge and training in the fields which must be covered. Although the most important requirement is an extensive knowledge of medicine and pathology, some knowledge of law and legal procedure is necessary. A knowledge of toxicology, chemistry and other sciences is of great importance also. Even an excellent pathologist cannot be expected to be capable in all these fields, certainly not in law. A competent lawyer with well trained medical assistants could do the work of the coroner's office properly. Certainly a man who is not trained in either medicine or law manifestly is unfit for this office.

The medical examiner system of New York City is headed by a noted pathologist assisted by other capable pathologists and toxicologists. The pathologist cooperates freely with the police, the district attorney, the courts, the state industrial board, the department of health and other departments. In return he receives cooperation and assistance from these departments. The work of the coroner's office is distributed, therefore, in somewhat the proper manner. More and better work has been done, more cooperation with other departments has occurred and more scientific use has been made of the pathologic material than ever before. The work has been accomplished on a smaller budget than that of the previous coroner system. Not only has the medical examiner established an example of excellence and efficiency never before achieved, but he has also set up a model to be followed. The quality of the work done by the medical examiner in New York cannot be improved. A larger budget, however, is

needed for a larger personnel, and for ampler facilities. In Boston, the medical examiner system, although not so excellent as that in New York, is a considerable improvement over the previous coroner system.

The work in some of the coroners' offices was found to be unbelievably poor, but it is unfortunate that individual investigators have described it in a sarcastic manner. This is, however, understandable, for it is often the natural reaction to find a terrible condition ludicrous. Certainly their observations fit into this category. Except for these lapses, so few as to be negligible, the entire report is on a firm, scientific, objective basis.

The individual investigators, whose names are too numerous to mention did an arduous and unpleasant task extremely well. The supplement on "Medical Testimony" by Professor Morgan is worthy of the attention of every physician and medical student.

The deductions and conclusions drawn in favor of the medical examiner system by the authors of the bulletin can be endorsed in their entirety; the suggestions and program deserve the serious consideration of every physician and of everyone working in the medical sciences.

BLOOD AND URINE CHEMISTRY. By R. B. H. GRADWOHL, M.D., Director of the Gradwohl Laboratories, St. Louis, and IDA E. GRADWOHL, A.B., Instructor in the Gradwohl School of Laboratory Technic. Price, $10. Pp. 544, with 117 illustrations and 4 color plates. St. Louis: C. V. Mosby Company, 1928.

This addition to the long list of manuals and works of reference already available to persons interested in the technic and interpretation of examination of the blood and urine seem to have been written with the object of presenting the subject in a more detailed and elementary fashion than has been attempted elsewhere.

The first and second sections of the book concern the routine of the analysis. The methods described are outlined fully and clearly, and represent a wise selection. The critical reader may regret, however, that the detailed procedures have not been given more point and meaning by the inclusion of brief expositions of the basic chemical and physical principles involved. The nine pages — and ten illustrations — devoted to the description of the Van Slyke procedure for the determination of the carbon dioxide combining capacity, for example, might well have contained some discussion of the gas laws. It is unfortunate that the usual tables of corrections for deviations in temperature and atmospheric pressure have been omitted. The reader is instructed that the use of such tables is "quite complicated," and that a sufficiently accurate result may be obtained by the simple expedient of subtracting 12 per cent from the uncorrected value indicated by the apparatus.

The third section, on the clinical interpretation of analyses of the blood and urine, has been poorly organized. Its lack of cohesion may be due, in part, to the fact that so much of the material has been quoted and, in part, to the fact that so little has been presented with reference to the physiologic and biochemical interrelations involved. The chapter is remarkably comprehensive and should prove valuable as a reference source.

The final section is devoted to the subject of basal metabolism. It is, with the exception of a few connecting paragraphs, quoted verbatim from other authorities.

VERERBUNG ANATOMISCHER VARIATIONEN DER NASE: IHRER NEBENHÖHLEN UND DES GEHÖRORGANS. VON DR. HANS LEICHER, Privatdozent, Oberarzt der Universitäts Hals Nasenklinik in Frankfurt am Main. Paper. Price, 21 marks. Pp. 164, with 64 illustrations. München: J. F. Bergmann, 1928.

This monograph includes 160 pages, with four additional pages devoted to an index of the literature. The author discusses the various aspects of anatomic variations in the structure of the nose, the paranasal sinuses and the organ of hearing. A perspective of ten special family groups is included. Special chapters contain a discussion of the hereditary aspect of the bridge, root, tip, nasal open-

ings, ala and other anatomic variations of the outer part of the nose. The hereditary features represented by the anatomic irregularities of the interior of the nose are discussed in a similar manner. Such variations are of special interest to the practicing physician, because of their clinical significance.

The author discusses the question of the hereditary factors in arrested pneumatization of the frontal sinuses. He considers the same question in relation to the mastoid process. This is of particular interest at present not only because of the suggested etiology from inflammation of the middle ear in the arrested pneumatization of the mastoid, but because of views concerning the particular menace from infection in these cases.

The author includes a study of the variations in the dimensions of the auricle, its prominence, the varieties of insertion, the Darwinian point; also other variations in the configuration of the auricle, the external meatus, the drum membrane and other portions. The clinician will find a discussion of many topics in which he is interested, such as the variations in the size and form of the mastoid process, the varieties of the digastric fossae, variations in the angle of the mastoid in the thickness of its outer cortex and variations in the course of the sigmoid sinus.

A HISTORY OF PATHOLOGY. By ESMOND R. LONG, Professor of Pathology, University of Chicago. With a Foreword by Fielding H. Garrison. Price, $5. Pp. 291, with 54 illustrations. Baltimore: Williams & Wilkins Company, 1928.

Colonel Garrison in his foreword welcomes this book as the first systematic account of the history of pathology in English. For his purpose the author considers his field to be the attempts to understand the nature of the deviations from normal health that one calls disease, and within the limits thus set he traces with admirable clearness the origins and growth of pathology. There are twelve chapters, the headings of which indicate the scope of the book: the pathology of antiquity; Galen and the middle ages; the pathology of the renaissance; the seventeenth century; Morgagni and the eighteenth century; the Paris school and the opening of the nineteenth century; pathology in England in the first half of nineteenth century; Rokitansky and the new Vienna school; Virchow and cellular pathology; pathological histology and the last third of the nineteenth century; the rise of bacteriology and immunology, and experimental and chemical pathology. These chapters give comprehensive yet compact and vivid accounts of the evolution of pathology and of the achievements and characteristics of its great pioneers. Here is indeed a competent and facile pen of unusual power. The historical continuity is sustained throughout with smoothness and ease. The illustrations are appropriate and instructive: There are facsimiles of important documents, portraits and copies of illustrations in pathologic classics. "Nothing," says the author, "gives a better perspective of the subject than an appreciation of the steps by which it has reached its present state." Long's book is recommended warmly to all who are interested in the evolution of pathology, and especially to medical students.

RÄTTSMEDICINSK SEKTIONSMETODIK, HANDBOK FÖR LÄKARE OCH STUDERANDE. GUNNAR HEDRÉN. Pp. 275. Stockholm: Nordiska Bokhandeln, 1928.

This small book gives an interesting and valuable insight into the medicolegal practice in Sweden. As in other countries, in Sweden the responsibility of making medicolegal autopsies is placed on many physicians who have not had special training in medicolegal jurisprudence, and the scope and procedure of such autopsies are prescribed in governmental regulations under the auspices of the bureau in the state government that deals with medical affairs. These regulations, on the basis of which Hedrén's book is based, might well be taken as model for more precise procedures than the methods followed at present in most parts of the United States. The Swedish regulations require that in all medicolegal necropsies the skull, brain and the organs of the neck, of the chest and of the abdomen must be examined, no matter what the condition in any one of these regions of the body may be found to be. The object is to secure thorough and complete examination in all cases. Special stress is laid on the external examination. The reg-

ulations also prescribe the manner in which the report of the results of the necropsy must be made. At the end of the book are given a few reports of necropsies which are highly instructive, but their value would have been increased by brief summaries at the end, giving the essential results and siginficance of the examination.

KLINISCHE LABORATORIUMSTECHNIK. HERAUSGEGEBEN VON PROF. DR. THEODOR BRUGSCH, Direktor der Medizinischen Klinik Halle a.S., und PROF. DR. ALFRED SCHITTENHELM, Direktor der Medizinischen Klinik Kiel. Zweite, vollständig neu bearbeitete Auflage der "Technik der Speziellen Klinischen Untersuchungsmethoden." Volume 3. Mit 144 Abbildungen, einer farbigen und einer schwarzen Tafel. Berlin: Urban & Schwarzenberg, 1928.

Not much more than the names of the editors remain from the first edition; even the name of the book is changed. This volume is arranged chiefly according to the organs tested, and contains chapters on function tests of the cardiovascular system (Frey), estimation of the blood pressure in the capillaries (Kylin), capillaroscopy (Weiss and Niekau), function tests of the lungs (Sonne), tests of the stomach and intestines (Retzlaff and van der Reis), the external pancreatic secretion (Schittenhelm and Chrometzka), the liver (Schellong), the biliary tract (Erbsen), kidney and tissues (Beckmann) and the endocrines (Zondek and Ucko). The methods used in examination of athletes are described by Bürger and the serology of cancer is discussed by Kappis. The book differs considerably from the old manuals of laboratory technic. At times it contains more physiology than technic. It is logical that it should also deal with clinical subjects, when the strictly clinical and the laboratory technic overlap. It is, however, difficult to imagine why a chapter on injection of animals with vital dyes and Rhoda Erdmann's good description of tissue cultures are added to a manual of clinical laboratory technic.

EXERCITATIO ANATOMICA DE MOTU CORDIS ET SANGUINIS IN ANIMALIBUS. By WILLIAM HARVEY, M.D. With an English Translation and Annotations by Chauncey D. Leake, Professor of Pharmacology, University of California. Tercentennial Edition. Price, $3.50. Springfield, Ill.: Charles C. Thomas, 1928.

This is an exceptionally noteworthy book that should receive wide appreciation. Part I is a facsimile reproduction by photo-engraving of the original edition in Latin of Harvey's "Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus," occupying some seventy-four pages. Part II is a new translation in the modern spirit by Professor Leake, with illuminating annotations. This part covers 132 pages. Harvey was a terse and vivid writer, and the new version reads well in its modern style. The translator presents an interesting postscript and an instructive chronology of the life of Harvey. There are ten appropriate illustrations and a useful index of the presentation. The book is beautifully printed and bound. Its sponsors are congratulated. They have produced a most worthy volume in celebration of the three hundredth anniversary of the publication of Harvey's immortal book.

THE BLOOD PLASMA IN HEALTH AND DISEASE. By J. W. PICKERING, D.Sc., Lecturer on Haematology, University of London, King's College. (Monographs of Medical and Surgical Science. Edited by Prof. R. J. S. McDowall, University of London, King's College.) Price, $4.25. Pp. 247. New York: The Macmillan Company, 1928.

This book will probably be found useful by all workers interested in the fundamental principles in the coagulation of blood as well as in the hemorrhagic diseases. An introductory chapter deals with the plasma proteins; the first half of the book contains a detailed discussion of the many complex factors involved in the coagulation of the blood and the current theories concerning them; the remainder of the book is devoted to the consideration of hemorrhages, thrombosis, menstrual blood and the hemorrhagic diseases. There are copious references to the original literature and an extensive bibliography covering all phases of the subjects presented.

Books Received

NEOPLASTIC DISEASES. A Treatise on Tumors. By James Ewing, A.M., M.D., Sc.D., Professor of Pathology at Cornell University Medical College, New York City; Pathologist to the Memorial Hospital. Third edition, revised and enlarged. Cloth. Pp. 1,127, with 546 illustrations. Philadelphia: W. B. Saunders Company, 1928.

This authoritative work has received a thorough revision. The chapter on tumors of bones has been rewritten and several new forms of such tumors are defined. The grouping of mammary carcinomas has been simplified. Tumors of the brain are discussed in the light of recent contributions to the study, and the newer nomenclature has been adopted in part. Throughout the book are evidences of careful revision of the text. About sixty new illustrations have been added, and the references to the literature have been verified. Needless to say, Ewing's great book will continue to occupy the commanding position in its field it has enjoyed from the first.

SCIENTIFIC REPORTS FROM THE GOVERNMENT INSTITUTE FOR INFECTIOUS DISEASES, THE TOKYO IMPERIAL UNIVERSITY. Director, Prof. Mataro Nagayo. For the Year 1927. Edited by Dr. Yoneji Miyagawa. Volume 6. Pp. 622. Tokyo: Shirokane-Daimachi, Shibaku.

The contents consist of original articles by members of the institute in the fields of bacteriology and serology, pathology, biology, biochemistry, clinical medicine, parasitology and protozoology, and medical entomology. The section on bacteriology and serology is the largest, occupying 253 pages. Some of the articles will be abstracted in the ARCHIVES.

FUNGI AND FUNGOUS DISEASES (Adolph Gehrmann Lectures of the University of Illinois College of Medicine, 1926). By Aldo Castellani, M.D. Pp. 203. Chicago: American Medical Association, 1928.

The three lectures deal with fungi, fungous diseases and skin diseases due to fungi. There are ninety-two illustrations. This work is an authoritative and valuable summary of the present knowledge in regard to fungi and fungous diseases.

A TEXTBOOK OF PATHOLOGY. By W. G. MacCallum, Professor of Pathology and Bacteriology, Johns Hopkins University, Baltimore. Fourth edition, revised. Pp. 1,177, with 606 illustrations. Cloth. Philadelphia: W. B. Saunders Company, 1928.

The book has been completely revised and in some parts practically rewritten in order that recent advances in knowledge might be included. Certain chapters dealing with matters with which the pathologist usually is not acquainted at first hand have been shortened or omitted. The new edition well maintains the high standards of its antecedents. The discussion is clear, comprehensive, pleasantly critical and stimulating. The influence of the book on the student is wholesome. The illustrations are admirable. The choice of objects, the drawing and the reproduction, including colors in the text, show special care. The work of the publisher is highly commendable.

GUTARTIGE RIESENZELLGESCHWÜLSTE. Eine vergleichend histologische Untersuchung von Privatdozent Dr. A. von Albertini, Prosektor des Pathologischen Institutes Zürich. Mit einem Vorwort von Professor Dr. H. v. Meyenburg. Price, 9 marks. Pp. 76, with 24 illustrations. Leipzig: Georg Thieme, 1928.

In this monograph, eleven cases of typical benign giant cell tumors are described in detail. These tumors are regarded as dysontogenic, mesenchymal growths, which do not form metastasis and are benign in character. In the cases described are

included giant cell growths of tendon sheaths, joints and the skin, with xanthomatous areas; such areas are regarded as secondary and due largely to local conditions. The author proposes to name this group of tumors "benign giant cell tumors."

METHODS AND PROBLEMS OF MEDICAL EDUCATION. Tenth series. Division of Medical Education. Pp. 343. New York: The Rockefeller Foundation, 1928.

Here are described a number of institutes of bacteriology, hygiene, public health, pathology, and pharmacology and physiology, as well as several medical libraries. "A limited distribution of these volumes or of separate reprints of the articles is made gratis upon request to The Rockefeller Foundation."

VERERBUNG ANATOMISCHER VARIATIONEN DER NASE IHRER NEBENHÖHLEN UND DES GEOHÖRORGANS. Von Dr. Hans Leicher, Privatdozent, Oberarzt der Universitäts Hals Nasenklinik in Frankfurt am Main. Paper. Price, 21 marks. Pp. 164, with 64 illustrations. Munich: J. F. Bergmann, 1928.

ANNUAL REPORT FOR THE YEAR 1927 OF THE SOUTH AFRICAN INSTITUTE FOR MEDICAL RESEARCH, JOHANNESBURG. Sir Spencer Lister, M.R.C.S. (Eng.), L.R.C.P. (Lond.), Director. Pp. 83. Johannesburg, 1928.

LABORATORY DIAGNOSIS AND EXPERIMENTAL METHODS IN TUBERCULOSIS. By Henry Stuart Willis, the Johns Hopkins University and Hospital. With a Chapter on Tuberculo-Complement Fixation by J. Stanley Woolley, Loomis Sanatorium, Loomis, N. Y. Introduction by Allen K. Krause, the Johns Hopkins University. Cloth. Price, $3.50. Pp. 330, with 25 illustrations. Springfield, Ill.: Charles C. Thomas, 1928.

THIRD REPORT OF COMMISSION ON MEDICAL EDUCATION, OCTOBER, 1928. Pp. 76.

Copies will be sent without charge to subscribers to the ARCHIVES on request to 215 Whitney Ave., New Haven, Conn.

HISTOLOGIE UND CHEMIE DER LIPOIDE DER WEISEN BLUTZELLEN UND IHRE BEZIEHUNG ZUR OXYDASEREAKTION, SOWIE ÜBER DEN STAND DER MODERNEN HISTOLOGIE DER ZELLIPOIDE. Von Dr. Ernst Sehrt. Price, 6 marks. Pp. 53, with 9 illustrations. Leipzig: Georg Thieme, 1927.

The author conclusively confirms the presence of lipoids in the granules of the polymorphonuclears. He had negative results with the lymphocytes, and little can be said about the monocytes, since he uses the ambiguous term "transitionals." The complete parallelism between the sudanophilic and the oxidase-bearing granules indicates in itself the significance of the lipoids for the oxidase reaction. Furthermore, the reaction disappears after the extraction of the blood film with reagents which destroy the sudanophilia of the granules, while the pure lipoids induce the oxidase reaction in vitro.

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